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(54) Title: 5-LIPOXYGENASE INHIBITORS

(57) Abstract

Hydroxyurea compounds comprising substituted and unsubstituted 1,2,3,4-tetrahydronaphthalene, indane, dihydrobenzofuran, 4H-2,3-dihydrobenzopyran, dihydrobenzothiophene, and indoline derivatives, pharmaceutical compositions containing said compounds, and their use as analgesics and 5-lipoxygenase pathway inhibitors.

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5-LIPOXYGENASE INHIBITORS

FIELD OF INVENTION

This invention relates to novel compounds, pharmaceutical compositions and methods for inhibiting oxygenated polyunsaturated fatty acid metabolism and disease states caused thereby. Specifically inhibited is the lipoxygenase enzyme pathway of arachidonic acid metabolism in an animal.

BACKGROUND OF THE INVENTION

The metabolism of arachidonic acid occurs by many pathways. One route of metabolism is via the cyclooxygenase (CO) mediated pathway which produces PGH_2 which is in turn metabolized to the prostanoids (PGE_2, TxA_2, and prostacyclin). These products are produced by various cells including polymorphonuclear leukocytes, mast cells and monocytes. Another route is by the lipoxygenase mediated pathway which oxidizes arachidonic acid initially to 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) which is further metabolized to LTA_4, the precursor to the peptidoleukotrienes (LTC_4, LTD_4, and LTE_4) and LTB_4. Additionally 5-HPETE is converted to 5-hydroxyeicosatetraenoic acid (5-HETE).

Lipoxygenases are classified according to the position in the arachidonic acid which is oxygenated. Platelets metabolize arachidonic acid to 12-HETE, while polymorphonuclear leukocytes (PMNs) contain 5 and 15 lipoxygenases. It is known that 12-HETE and 5,12-diHETE are chemotactic for human neutrophils and eosinophils, and may augment the inflammation process. 5-HPETE is known to be a precursor to the peptidylleukotrienes, formerly known as slow reacting substance of anaphylaxis (SRS-A) and LTB_4. The SRS family of molecules, such as leukotrienes C_4 and D_4 have been shown to be potent bronchoconstrictors. LTB_4 has been shown to be a potent chemotatic for PMNs. The products of the 5-lipoxygenase pathway are believed to play an important role in initiating and maintaining the inflammatory response of asthma, allergy, arthritis,

psoriasis, and inflammatory bowel disease. It is believed that blockage of this enzyme will interrupt the various pathways involved in these disease states and as such inhibitors should be useful in treating a variety of inflammatory diseases, such as those inumerated above. The absence of selective inhibitors of lipoxygenase, as opposed to cyclooxygenase, which are active in vivo has prevented adequate investigation of the role of leukotrienes in inflammation.

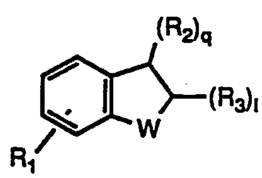
The arachidonic acid oxygenated products, as noted above, have been identified as mediators of various inflammatory conditions. The various inflammatory disease states caused by these mediators and many other conditions, as discussed herein, are all conditions in which an oxygenated polyunsaturated fatty acid metabolite inhibitor, such as a 5-LO inhibitor, would be indicated.

There remains a need for treatment, in this field, for compounds which are capable of inhibiting the oxygenation of arachidonic acid by inhibition of enzymes such as lipoxygenase, specifically 5-lipoxygenase (5-LO) thereby preventing the formation of various leukotrienes and prostaglandins.

The compounds of Formula (I) have been found to be not only be selective 5-lipoxygenase inhibitors but also, unexpectantly, to possess analgesic activity, not normally associated with compounds having lipoxygenase inhibition.

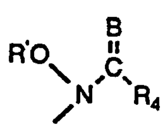
SUMMARY OF THE INVENTION

This invention relates to a compound of the Formula (I)



FORMULA (I)

wherein

R_2 and R_3 are  ;

R' is hydrogen, a pharmaceutically acceptable cation, aroyl or a C_{1-12} alkoyl;

B is oxygen or sulfur;

R_4 is NR_5R_6, alkyl $_{1-6}$, halosubstituted alkyl $_{1-6}$, hydroxy substituted alkyl $_{1-6}$, alkenyl $_{2-6}$, aryl or heteroaryl optionally substituted by halogen, alkyl $_{1-6}$, halosubstituted alkyl $_{1-6}$, hydroxyl, or alkoxy $_{1-6}$;

R_5 is H or alkyl$_{1-6}$;

R_6 is H, alkyl$_{1-6}$, aryl, arylalkyl $_{1-6}$, heteroaryl, alkyl substituted by halogen or hydroxyl, aryl or heteroaryl optionally substituted by a member selected from the group

consisting of halo, nitro, cyano, $alkyl_{1-12}$, alkoxy $_{1-6}$, halosubstituted $alkyl_{1-6}$, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R_5 and R_6 may together form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen;

W is $CH_2(CH_2)_s$, $O(CH_2)_s$, $S(CH_2)_s$, or $NR_7(CH_2)_s$;

R_7 is hydrogen, C_{1-4} alkyl, phenyl, C_{1-6} alkoyl, or aroyl;

s is a number having a value of 0 to 3; provided that when l is 1 and W is $O(CH_2)_s$, $S(CH_2)_s$, then s is 1 to 3; and when W is $NR_7(CH_2)_s$ then s is 1 to 3 and q is 1;

q is a number having a value of 0 or 1;

l is a number having a value of 0 or 1;

provided that when q is 0 then l is 1 and R_2 is hydrogen; and when q is 1 then l is 0 and R_3 is hydrogen;

R_1 is a member selected from the group consisting of hydrogen, $alkyl_{1-10}$, $alkoxy_{1-10}$, naphthyl, $(CH_2)_m$-Ar-$(X)_v$, $(CH_2)_m(C{=}C)_n(CH_2)_p$-Ar-$(X)_v$, $O(CH_2)_m$Ar-$(X)_v$, $S(CH_2)_m$-Ar-$(X)_v$, or $N(CH_2)_m$-Ar-$(X)_v$;

p is a number having a value of 0 to 3;

m is a number having a value of 0 to 3;

n is a number having a value of 0 to 3;

v is a number having a value of 0 to 3;

Ar is a member selected from the group consisting of phenyl, naphthyl, quinolyl, isoquinolyl, pyridyl, furanyl, imidazoyl, benzimidazoyl, triazolyl, oxazolyl, isoxazolyl, thiazole, or thienyl;

X is a member selected from the group consisting of hydrogen, halogen, alkyl $_{1-10}$, cycloalkyl $_{5-8}$, alkenyl $_{2-10}$, hydroxy, $(CHY)_t$carboxy, O-alkyl $_{1-10}$, $S(O)_r$ $alkyl_{1-10}$, aryloxy, $arylalkyl_{1-6}$ oxy, halosubstituted $alkyl_{1-6}$, hydroxy substituted $alkyl_{1-6}$, $(CHY)_tN(R_5)_2$, or cyano; provided that if v is a number greater than 1 then one substituent must be selected from alkyl, O-alkyl $_{1-10}$, or halo;

r is 0 to 2; Y is hydrogen or $alkyl_{1-3}$;

t is 0 or 1; provided that when q is 1, R_4 is NR_4R_5, W is $CH_2(CH2)_s$, and s is 1, then R_1 is other than hydrogen, $alkyl_{1-10}$, or alkoxy $_{1-10}$;

and the pharmaceutically acceptable salts thereof.

This invention also relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and an effective, non-toxic 5-lipoxygenase pathway inhibiting amount of a compound of the Formula (I) as defined above, or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of treating an oxygenated polyunsaturated fatty acid (hereinafter OPUFA) mediated disease in an animal in need thereof which comprises administering to such animal, an effective amount of a compound of Formula (I) or pharmaceutically acceptable salts thereof.

More specifically this invention relates to a method of treating a lipoxygenase pathway mediated disease in an animal in need thereof which comprises administering to such animal an effective, non-toxic lipoxygenase pathway inhibiting amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention further relates to a method of treating algesia in an animal in need thereof which comprises administering to such animal an effective, analgesic amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above, pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent and a compound of Formula (I) and pharmaceutically acceptable salt thereof, methods of treating an OPUFA mediated disease, specifically a 5-lipoxygenase pathway mediated disease comprising administration of a compound of Formula (I) and salts thereof, and methods of treating algesia comprising administration of a compound of Formula (I), and salts thereof.

The compounds of Formula (I) have been found to be useful in inhibiting the enzymes involved in the oxygenated polyunsaturated fatty acid pathway which includes the metabolism of arachidonic acid, in an animal, including humans; in need thereof. The compounds of Formula (I) have oral activity and are therefore useful for the treatment of various inflammatory disease states. The compounds of Formula (I), particularly the hydroxyurea derivatives, also possess unexpectedly, a superior analgesic activity, thus providing a method of treatment for algesia in an animal in need thereof. The genus of compounds of Formula (I) useful in the treatment of algesia and as inhibitors of the OPFUA pathway does include compounds wherein q is 1, R_4 is NR_4R_5, W is $CH_2(CH2)_s$, s is 1, and R_1 is hydrogen, alkyl$_{1-10}$, or alkoxy $_{1-10}$.

A preferred embodiment of the present invention is where R_1 is selected from $O(CH_2)_m$-Ar-$(X)_v$, $(CH_2)_m$-Ar-$(X)_v$, or $S(CH_2)_m$-Ar-$(X)_v$; m is a number having a value of 0 to 3; and v is a number having a value of 1 to 2. Preferred X groups are hydrogen, alkoxy, halo, and CF_3, preferrably in the 4-position. When X is $(CHY)_tN(R_5)_2$ the R_5 group is independently selected from hydrogen or an alkyl of 1-6 carbons yielding an unsubstituted, mono- or di-substituted amine component.

Specific R_1 groups of interest are alkoxy, phenethyl, benzyloxy, aryloxy, and substituted derivatives thereof. Specifically such groups are methoxy, phenoxy, benzyloxy, 4-methoxybenzyloxy, 4-chlorobenzyloxy, 4-flurophenoxy, 2-phenylethyl, 2-

quinoylmethoxy, and 2-naphthylmethoxy. A more preferred embodiment of this invention is where W is $CH_2(CH_2)_s$ or $O(CH_2)_s$ and s is a number having a value of 0 or 1.

A further preferred embodiment of the present invention is where B is oxygen. Preferred R_4 substituent groups are NR_5R_6 and the alkyl hydroxamate derivatives. Preferred R_6 substitutions when R_6 is aryl or arylalkyl are phenyl or benzyl. A more preferred embodiment is where R_5 and R_6 are independently hydrogen or alkyl. Most preferred is where q is 1 and l is 0 for all R_2 and R_3 substitutent groups and W terms.

A preferred ring placement when W is $CH_2(CH_2)_s$ and s is 1 is on the 5- or 6-position of the benzene ring and when s is 0 the preferred position is the 4- or 5-position; applicable substitution patterns are also preferred when W is $O(CH_2)_s$, i.e., when s is 1, the 7- or 8- position, and when s is 0 the 6- or 7- position.

When R_4 is other than a NR_5R_6 moiety yielding a hydroxamate derivative, R_4 is preferrably alkyl, more preferably C1-6, such as methyl, ethyl, n-propyl, isopropyl or t-butyl all optionally substituted; B is oxygen and q is 1. More preferred is where W is $CH_2(CH_2)_s$ or $O(CH2)_s$ and s is 0 or 1. For all compounds herein, R' is preferably hydrogen or a pharmaceutically acceptable cation.

Some preferred hydroxyurea compounds of Formula (I) compounds which are themselves within the scope of the present invention include the following:

N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-[5-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(6-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-[6-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(1,2,3,4-Tetrahydronaphthyl)-N-hydroxyurea;
N-1-[6-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Phenethyl)-1,2,3,4-tetrahydronapthyl]-N-hydroxyurea;
N-1-[6-(2-Quinolinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Pyridinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Benzimidazolylmethoxy)-(1,2,3,4-tetrahydronaphthyl)]-N-hydroxyurea;
N-2-(7-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(7-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(6-Phenyl-1,2,3,4-tetrahydronapthyl)-N-hydroxyurea;
N-1-(5-Benzyloxyindanyl)-N-hydroxyurea; N-1-(5-Phenoxyindanyl)-N-hydroxyurea;
N-1-(5-(4-Flurophenoxyindanyl)-N-hydroxyurea;

N-1-(4-Benzyloxyindanyl)-N-hydroxyurea;
N-1-(4-Phenoxyindanyl)-N-hydroxyurea;
N-1-(4-(4-Flurophenoxyindanyl)-N-hydroxyurea;
N-1-[5-(4-methoxybenzyloxy)-indanyl]-N-hydroxyurea;
N-1-(7-Phenoxyindanyl)-N-hydroxyurea;
N-3-(7-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyurea;
N-3-[7-(4-Flurophenoxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-3-(7-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyurea;
N-3-(6-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyurea;
N-3-[6-(4-Flurophenoxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-3-(6-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyurea; or
N-3-[6-(4-Methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

Preferred hydroxamate derivatives of Formula (1) compounds which are within the scope of the present invention are:

N-Hydroxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]acetamide;
N-Hydroxy-N-[1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)]acetamide;
N-Hydroxy-N-[1-(5-benzyloxyindanyl)]acetamide;
N-Hydroxy-N-1-(6-methoxy-1,2,3,4-tetrahydronaphthyl)acetamide;
N-Hydroxy-N-1-(1,2,3,4-tetrahydronaphthyl)acetamide;
N-Hydroxy-N-1-[6-(4-methoxybenzyl)oxy-1,2,3,4-tetrahydronaphthyl]acetamide;
N-Hydroxy-N-1-[6-(4-chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]acetamide;
N-Hydroxy-N-1-[6-(2-naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]acetamide;
N-Hydroxy-N-3-(6-benzyloxy-2,3-dihydrobenzofuranyl)acetamide;
N-Hydroxy-N-1-[6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]acetamide;
N-Hydroxy-N-2-(7-methoxy-1,2,3,4-tetrahydronaphthyl)acetamide;
N-Hydroxy-N-1-(7-benzyloxy-1,2,3,4-tetrahydronaphthyl)acetamide;
N-Hydroxy-N-[1-(6-phenyl-1,2,3,4-tetrahydronaphthyl)]acetamide;
N-Hydroxy-N-1-[5-(4-methoxybenzyloxy)indanyl]acetamide;
N-Hydroxy-N-3-[6-(4-methoxybenzyloxy)-2,3-dihydrobenzofuranyl]acetamide;
N-Hydroxy-N-1-(5-benzyloxy-1,2,3,4-tetrahydronaphthyl)acetamide;.
N-Hydroxy-N-1-(6-phenoxy-1,2,3,4-tetrahydronaphthyl)]acetamide;
N-Hydroxy-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)propionamide;
N-Hydroxy-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthylbenzamide;
N-Hydroxy-N-1-[6-(2-phenethyl)-1,2,3,4-tetrahydronaphthyl]-2,2-dimethylpropionamide.

As the hydroxamates and hydroxyureas disclosed herein are made thru a common intermediate, a hydroxylamine deriviatives of Formula (II), any N-hydroxy acetamide derivatives of the corresponding hydroxyamines made herein are also considered a preferred embodiment of this invention.

Patricularly preferred hydroxyamines of Formula (II) are
N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-[5-(4-Flurophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine;
N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-(6-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-[6-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine; or
N-1-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-(1,2,3,4-Tetrahydronaphthyl)-N-hydroxyamine;
N-1-[6-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine;
N-1-[6-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine;
N-1-[6-(2-Naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine;
N-1-[6-(2-Phenethyl)-1,2,3,4-tetrahydronapthyl]-N-hydroxyamine;
N-1-[6-(2-Quinolinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine;
N-1-[6-(2-Pyridinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine;
N-1-[6-(2-Benzimidazolylmethoxy)-(1,2,3,4-tetrahydronaphthyl)]-N-hydroxyamine;
N-2-(7-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-(7-Benzyloxy-1,2,3,4,-tetrahydronaphthyl)-N-hydroxyamine;
N-1-(6-Phenyl-1,2,3,4-tetrahydronapthyl)-N-hydroxyamine;
N-1-(5-Benzyloxyindanyl)-N-hydroxyamine; N-1-(5-Phenoxyindanyl)-N-hydroxyamine;
N-1-(5-(4-Flurophenoxyindanyl)-N-hydroxyamine;
N-1-(4-Benzyloxyindanyl)-N-hydroxyamine; N-1-(4-Phenoxyindanyl)-N-hydroxyamine;
N-1-(4-(4-Flurophenoxyindanyl)-N-hydroxyamine;
N-1-[5-(4-methoxybenzyloxy)-indanyl]-N-hydroxyamine;
N-1-(7-Phenoxyindanyl)-N-hydroxyamine;
N-3-(7-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine;
N-3-[7-(4-Flurophenoxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine;
N-3-(7-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine;
N-3-(6-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine;
N-3-[6-(4-Flurophenoxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine; or
N-3-(6-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine;
N-3-(6-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine;
N-3-[6-(4-Methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine; or
N-3-(7-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine.

The terms "aryl" or "heteroaryl" are used herein at all occurrences to mean substituted and unsubstituted aromatic ring(s) or ring systems containing from 5 to 16 carbon atoms, which may include bi- or tri-cyclic systems and may include, but are not

limited to heteroatoms selected from O, N, or S. Representative examples include, but are not limited to, phenyl, naphthyl, pyridyl, quinolinyl, thiazinyl, and furanyl.

The terms "lower alkyl" or "alkyl" are used herein at all occurrences to mean straight or branched chain radical of 1 to 10 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms,unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term "aralkyl" is used herein to mean C_{1-4} Ar, wherein Ar is as defined in Formula (I).

The term "aroyl" is used herein to mean - C(O) Ar, wherein Ar is as defined in Formula (I), including, but not limited to benzyl, 1- or 2-naphthyl and the like.

The term "alkoyl" is used herein to mean $-C(O)C_{1-10}$, wherein alkyl is as defined above, including but not limited to methyl, ethyl, isopropyl, n-butyl, t-butyl, and the like.

The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.

The term "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements fluorine, chlorine, bromine, and iodine.

The term "lipoxygenase" is used herein to mean 5-, 12-, or 15- lipoxygenase, preferably 5-lipoxygenase.

By the term "OPUFA mediated disease or disease state" is meant any disease state which is mediated (or modulated) by oxidized polyunsaturated fatty acids, specifically the arachidonic acid metabolic pathway. The oxidation of arachidonic acid by such enzymes as the lipoxygenase enzymes is specifically targeted by the present invention. Such enzymes include, but are not limited to, 5-LO, 12-LO, and 15-LO; which produce the following mediators, including but not limited to, LTB_4, LTC_4, LTD_4, 5,12-diHETE, 5-HPETE, 12-HPETE, 15-HPETE, 5-HETE,12-HETE and 15-HETE.

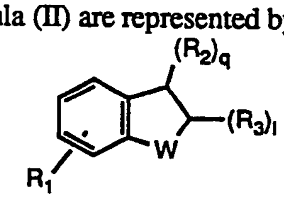
By the term "OPUFA interfering amount" is meant an effective amount of a compound of Formula (I) or (II) which shows a reduction of the <u>in vivo</u> levels of an oxgyenated polyunsaturated fatty acid, preferably an arachidonic acid metabolite.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention. Specifically exemplified compounds are the pairs, (+)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea, and (-)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea; and

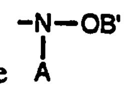
(+)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea and (-)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea.

Useful intermediates of the present invention are the novel hydroxylamine derivatives of Formula (II) as represented by the formula below. The compounds of Formula (II) have also been found to be compounds useful for inhibition of the OPUFA pathway and in the treatment of algesia. The genus of compounds of Formula (II) useful as OPUFA inhibitors or in the treatment of algesia include compounds wherein B is hydrogen, W is $CH_2(CH_2)_s$ and s is 0 or 1, and compounds wherein B is hydrogen, W is $S(CH_2)_s$ and s is 1".

The compounds of Formula (II) are represented by the structure:



FORMULA (II)

wherein R_2 and R_3 are  ;

B' is hydrogen, benzyl, optionally substituted benzyl , $Si(R_x)_3$, $C(O)R_{5'}$, $C(O)OR_{5'}$, $CH_2OCH_2CH_2Si(CH_3)_3$, C_1alkyl-C_{1-3}alkoxy, C_1alkylC_2alkoxyC_{1-3}alkoxy, or tetrahydropyranyl ;

A is hydrogen or $C(O)OR_Z$;

R_Z is benzyl, $Si(R_x)_3$, t-butyl, or $CH_2OCH_2CH_2Si(Rx)_3$;

$R_{5'}$ is C_{1-6} alkyl, aryl, or aralkyl;

R_x is independently selected from alkyl or aryl; and the remaining variables R_1, W, Ar, X, Y, R_5, R_7, m, n, p, s, t , q; l, and v are as defined above for Formula (I); provided that when B is hydrogen, W is other than $CH_2(CH_2)_s$, and s is 0 or 1, and B is hydrogen, W is other than $S(CH_2)_s$ and s is 1.

Preferred B substituent groups are tetrahydropyranyl; CH_2OCH_3 when B is C_1alkylC_{1-3}alkoxy; $CH_2OCH_2CH_2Si(CH_3)_3$, $CH_2OCH_2CH_2OCH_3$ when B is C_1alkylC_2alkoxyC_{1-3}alkoxy; $C(O)R_{5'}$ and $C(O)0R_{5'}$ with $R_{5'}$ as a C_{1-6} alkyl, specifically methyl, t-butyl, or phenyl.group and benzyl when R_5 is an aralkyl group. When B is an optionally substituted benzyl the substituent groups are selected from C_{1-6} alkoxy or C_{1-6} alkyl.

The hydroxylamine derivatives of Formula II are easily converted to the compounds of Formula (I) wherein R_4 is NHR_5R_6 or a hydroxamate derivative using art known

proceedures. Various illustrative methods to prepare compounds of Formula (I) are given in U.S. Patent Summers et al., 4,873,259, issued October 10, 1989, pages 7-11 whose disclosure is incorporated by reference herein.

The present compounds of Formula (I) can be prepared by art-recognized procedures from known compounds. Several different synthetic schemes can be used to prepare the compounds of this invention and are described in greater detail below. Although the schemes when illustrated utilize only one particular compound, the 1,2,3,4-tetrahydronaphthalene derivative, it will be seen from the working examples that other compounds of this invention can be prepared in the same manner using the appropriate starting materials, such as 6-methoxy-1-tetralone, 6-methoxy-2-tetralone, 5-hydroxy-2-tetralone, 7-methoxy-2-tetralone, 5-methoxy-indan-1-one, or 7-methoxybenzo-cycloheptan-1-one. Many additional starting materials are readily available to one skilled in the art, including but not limited to, the various mono- and di-substituted 3-chromanones or 4-chromoanones or 3-hydroxybenzofuranones, as disclosed in Heterocyclic Compounds: Chromenes. Chromanones. and Chromones. Chapters 3 and 4, Ellis Ed., Interscience Publication, Wiley & Sons, New York, or in The Chemistry of Heterocyclic Compounds , Weissberger, A. and Taylor, E. , Editors, Interesciene Publication, Wiley & Sons, New York, Mustafa, A. , Chapter V. Benzofuranones.

As a general summary of the synthetic pathways described in greater detail below the compounds of Formula (I) and (II) can be produced by the following means:

The compounds of Formula (I) can be produced by a process which comprises

A. reacting a compound of Formula (II) as described above, wherein B is hydrogen,

(i) with trimethylsilyl isocyanate (TMSNCO), followed by work up with ammonium chloride to yield a hydroxyurea derivative of a Formula (I) compound wherein R_4 is NH_2; or

(ii) with sodium or potassium cyanate in an acidic solution to yield a hydroxyurea derivative of a Formula (I) compound wherein R_4 is NH_2; or

(iii) with gaseous HCl, followed by treatment with phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate; which is reacted with aqueous ammonia, or a substituted amine to yield an optionally substituted hydroxyurea derivative of a Formula (I) compound; or

(iv) with acetyl chloride and organic solvent, such as triethylamine, to yield the N,O-diacetate derivative followed by hydrolysis with an alkali hydroxide, such as lithium hydroxide, to yield a compound of Formula (I) wherein R_4 is other than NR_5R_6; or

(v) with an acylating agent, such as acetic anhydride in the presence of a base, such as pyridine, followed by hydrolysis with an alkali hydroxide, such as lithium hydroxide, to yield a compound of Formula (I) wherein R_4 is a hydroxamic acid derivative; or

B. reacting a compound of Formula (II) as described above, wherein B is a benzyl, substituted benzyl or a benzyl carbonate protecting group, with

(i) acetyl chloride in an organic solvent to yield a protected hydroxamic acid derivative of Formula (I) compounds, which is then deprotected, optionally by hydrogenation or with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I) wherein R_4 is other than NR_5R_6; or

(ii) trimethylsilyl isocyanate as in step A above, to yield protected hydroxyurea derivatives of Formula (I) compounds which is then deprotected, optionally by hydrogenated with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I); or

(iii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine; which is then deprotected, optionally by hydrogenation or with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I); or

(iv) sodium or potassium cyanate in an acidic solution which is then deprotected, optionally by hydrogenation or with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I); or

C. reacting a compound of Formula (II) as described above, wherein B is is $Si(R_x)_3$, or $CH_2OCH_2CH_2Si(Rx)_3$ with

(i) sodium or potassium cyanate in an acidic solution and deprotected by use of anhydrous fluoride $(R_4N^+)F^-$, or under mildly acidic conditions, to yield the corresponding compounds of Formula (I); or

(ii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine; which is deprotected by use of anhydrous fluoride $(R_4N^+)F^-$, or under mildly acidic conditions; to yield the corresponding compounds of Formula (I); or

(iii) trimethylsilyl isocyanate and deprotected by use of anhydrous fluoride $(R_4N^+)F^-$, or under mildly acidic conditions; to yield the corresponding compounds of Formula (I); or

(iv) acetyl chloride in organic solvent which is then deprotected by use of anhydrous fluoride $((R_4N^+)F^-$, or under mildly acidic conditions, to yield the corresponding compounds of Formula (I); or

D. reacting a compound of Formula (II) as described above, wherein B is tetrahydropyranyl, C_1alkyl-C_{1-3}alkoxy, or C_1alkylC_2alkoxyC_{1-3}alkoxy, with

(i) sodium or potassium cyanate in an acidic solution, and deprotected by a mild acid treatment, such as pyridinium para-toulenesulphonate in methanol or dilute HCl to yield the corresponding compounds of Formula (I); or

(ii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine; and deprotected by a mild acid treatment, such as pyridinium para-toulenesulphonate in methanol or dilute HCl; to yield the corresponding compounds of Formula (I); or

(ii) with trimethylsilyl isocyanate, then deprotected by a mild acid treatment, such as pyridinium para-toulenesulphonate in methanol or dilute HCl; to yield the corresponding compounds of Formula (I); or

(iii) with acetyl chloride in organic solvent which is then deprotected by a mild acid treatement, such as pyridinium para-toulenesulphonate in methanol or dilute HCl to yield the corresponding compounds of Formula (I); or

E. reacting a compound of Formula (II) as described above, wherein B is t-butyloxycarbonyl with

(i) sodium or potassium cyanate in an acidic solution, and deprotected by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or with anhydrous ether HCl; or

(ii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine; and deprotected by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or with anhydrous ether HCl; to yield the corresponding compounds of Formula (I); or

(iii) with trimethylsilyl isocyanate and then deprotected, optionally with ethane thiol in the presence of aluminium trichloride by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or anhydrous ether HCl; to yield the corresponding compounds of Formula (I); or

(iv) with acetyl chloride in organic solvent which is then deprotected, optionally with ethane thiol in the presence of aluminium trichloride; or by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or anhydrous ether HCl to yield the corresponding compounds of Formula (I); or

F. reacting a compound of Formula (II) as described above, wherein B is an alkoyl or aroyl with

(i) sodium or potassium cyanate in an acidic solution and deprotected with a suitable base, such as potassium carbonate; to yield the corresponding compounds of Formula (I); or

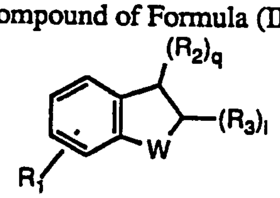
(ii) with trimethylsilyl isocyanate and deprotected with a suitable base, such as potassium carbonate; to yield the corresponding compounds of Formula (I); or

(iii) with acetyl chloride in organic solvent which is then deprotected by treatment with a suitable base, such as potassium carbonate; to yield the corresponding compounds of Formula (I).

The compounds of Formula (II) can be produced by a process which comprises

A process for producing a compound of the Formula (II) as defined above, which process comprises

A. reacting a compound of Formula (III)

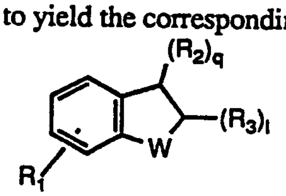


(III)

wherein R_2 and R_3 are =O;

W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);

with hydroxylamine in solvent to yield the corresponding oxime derivative of Formula (IV)



(IV)

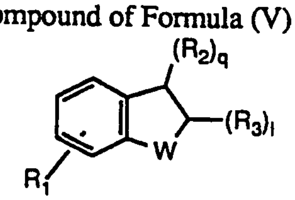
wherein R_2 and R_3 are =N-OH;

W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);

which is then reduced with borane pyridine complex, borane trimethylamine, or borane tetrahydrofuran or other borane complexes, to yield the hydroxylamine derviatives of Formula (II); or

B. reacting a compound of Formula (IV) as defined above with sodium cyanoborohydride or phenyldimethylsilane in anhydride in trifluroacetic acid to yield the hydroxylamine derviatives of Formula (II); or

C. reacting a compound of Formula (V)



(V)

wherein R_2 and R_3 are X;

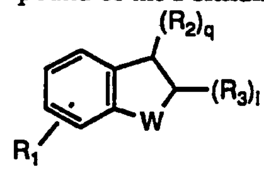
X is a leaving group, such as a halogen, tosylate, mesylate or a triflate moiety;

W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);

with Z-furfulaldehyde oxime and base to yield the corresponding nitrone of Formula (VI) which is hydroylzed to yield the corresponding hydroxylamine derviatives of Formula (II);

D. reacting a compound of Formula (V) as described above, with a protected hydroxylamine to yield the corresponding protected hydroxylamine of Formula (II); or

E. reacting a compound of the Formula (VI)

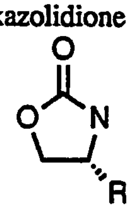


(VI)

wherein R_2 and R_3 are OH;
W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II) as described above; with a protected hydroxylamine, such as N,O-bis(t-butyloxycarbonyl)-hydroxylamine) or bisbenzyloxycarbonyl, and triphenylphosophine/ diethyldiazodicarboxylate to produce an intermediate which is treated with acid to yield the hydroxylamines of Formula (II).

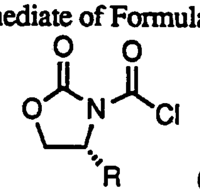
The homochiral compounds of Formula (I), as well as the homochiral intermediates of Formula (II) can be prepared by a process which comprises

A. (i) reacting a homochiral oxazolidione of Formula (A)



(A)

wherein R is an optionally substituted aryl, arylmethyl, heteroaryl, or heteroarylmethyl; with phosgene or a phosgene equivalent and a base in anhydrous solvent to yield to form the corresponding acid chloride intermediate of Formula (VII)



(VII)

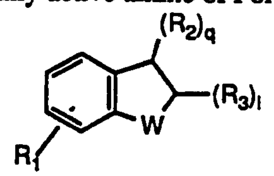
(ii) reacting the Formula (VII) adduct with a chloronated hydrocarbon or etheral solvent and base to yield the corresponding (+) and (-) compound of Formula (II);

(iii) cleaving the adducts under basic conditions to yield the individual entantiomers of the Formula (II) compounds; or

B. reacting an optically active alcohol of Formula (VI) as defined above, with N,O-bis(t-butyloxycarbonyl)hydroxylamine) and triphenylphosophine/ diethyldiazodicarboxylate to produce an intermediate which is treated with acid to yield the hydroxylamines of Formula (II); or reacting the corresponding optically active halo or sulfonates of Formula (VI),which

may be optionally protected with a base, such as triethylamine, or pyridine; are then optionally deprotected to yield the formula (II) compounds, which are optionally reacted under any of the various pathways described herein to yield optically active final compounds of Formula (I); or

C. (i) reacting an optically active amine of Formula (VIII)



(VIII)

wherein R_2 and R_3 are NH_2;
W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);
with 4-methoxybenzaldehyde in trimethylamine;

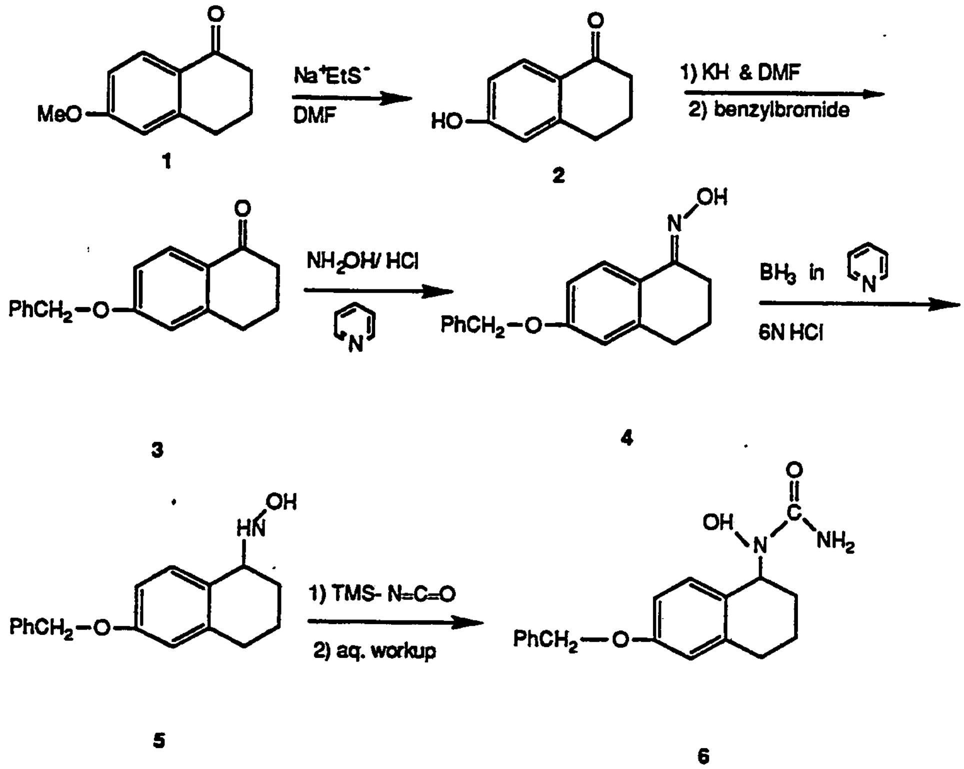
(ii) oxidizing the intermediate of step (i) to yield the corresponding oxaziridine;

(iii) reacting the oxaziridine of step (ii) under acid conditions to yield the hydroxylamine salts of Formula (II) compounds; and then optionally reacting under the various pathways described herein to yield optically active final compounds of Formula (I); or

D. reacting the optically active amine of Formula (VIII) as described above with dimethyldioxirane or a peracid anhydride, such as benzoyl peroxide, to yield the protected chiral hydroxylamine of Formula (II) compounds; which may be optionally deprotected to yield the final compounds of Formula (II); and optionally reacted by the various pathways described herein to yield optically active final compounds of Formula (I); or

E. reacting the optically active alcohol of Formula (VI) as described above with diphenylphosphoryl azide and triphenylphosphine / diethyldiazodicarboxylate (DEAD) producing the optically active azide intermediate which can be reduced to produce the optically active amine used in Step C, parts (i) and (ii) above; and optionally reacted by the various pathways described herein to yield optically active final compounds of Formula (I).

The compounds of Formula (I) can be prepared according to the following synthetic route, as displayed in Scheme I below :

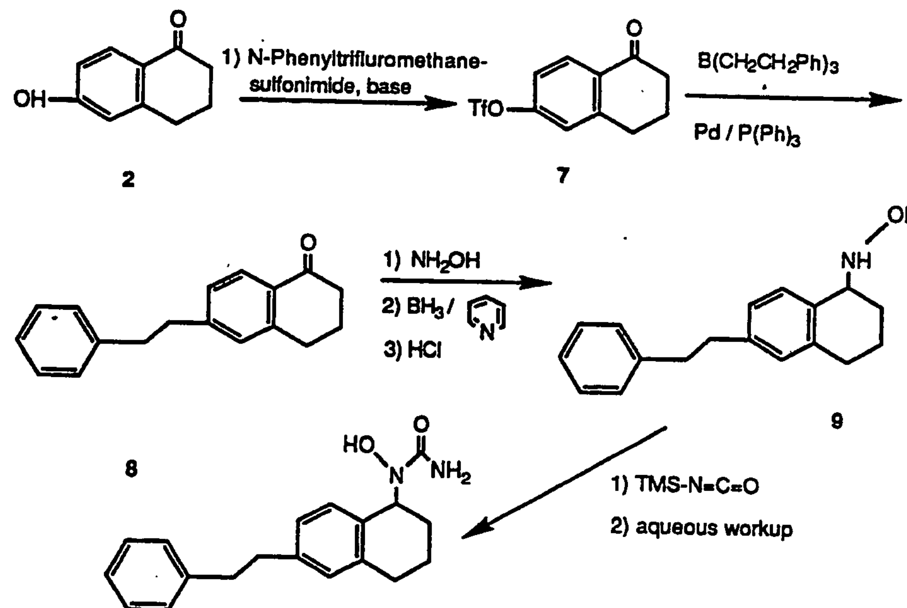


SCHEME I

In scheme I, compound 1 or any other suitable alkoxy derivative may be treated by a known means to remove the alkyl portion of the alkoxy group, such as using a solution of sodium ethanethiolate in a solvent, such as dry DMF, to which the alkoxy derivative is added and heated. Following concentration of the reaction and addition of an organic solvent, such as ethyl acetate, an aqueous acidic workup yields the corresponding hydroxy derivative 2. The hydroxy compound 2 is then treated with a metal hydride, such as potassium hydride, and after the gas evolution subsides, a benzylhalide or phenylethyl halide, such benzylbromide, is added. After stirring and concentrating, the residue is dissolved in an organic solvent , such as ethyl acetate, and washed with acid, preferably hydrochloric, to yield after a standard aqueous workup the benzyloxy derivative 3. Compound 3 is then converted to the corresponding oxime 4 by addition of hydroxylamine hydrochloride in a solvent, such as pyridine and heated for about 30 minutes to about 2 hours. The oxime 4 is reduced to the corresponding hydroxylamine 5 by addition of a borane/pyridine complex to which is added, after stirring an acidic solution, preferably 6N HCl. Borane dimethylsulfide in tetrahydrofuran may also be used. Addition of an alkali metal hydroxide, such as NaOH, and extraction into an organic solvent , for example ethyl ether or CH_2Cl_2, yields the hydroxylamine 5. The hydroxylamine is converted to the corresponding hydroxyurea 6 by addition of trimethysilylisocyanate and heating followed by an aqueous/organic workup.

The hydroxamates can also be produced in a similar manner from the same intermediate **5** which is then converted to a diacetate intermediate by addition of an acylating agent, such as acetyl chloride (about 2 equivalents), with triethylamine (about 3 equivalents) in methylene chloride for about 30 minutes. Acetic anhydride in the presence of other bases such as pyridine will also work. The O-acetate moiety is removed by hydrolysis with an alkali metal hydroxide, such as lithium hydroxide, to yield the corresponding hydroxamic acid of Formula (I). The oxime **4** or O-protected derivatives, such as the acetate, may also be reduced by borane-trimethylamine, borane-tetrahydrofuran, sodium cyanoborohydride in methanol, or other borane compounds.

Another synthetic route to prepare the compounds of Formula (I) is described in Scheme II, illustrated below.



SCHEME II

The hydroxytetralone derivative **2** is modified to contain an active leaving group, such as the triflate indicated in **7**. Other acceptable leaving groups are the bromides, chlorides, iodides, tosylates, and mesylates. Using a bidentate Pd (II) catalyst, such as $PdCl_2$ (dppf) or $Pd(PPh_3)_4$, or any other acceptable coupling agent, and a tris(phenethyl)-borane derivative, using the method of Sukuki (A. Suzuki et. al. J.A.C.S., 111, pgs.314-321, 1989) results in the addition of the appropriate R_1 group to yield the corresponding tetralone compound **8**. The above cited procedure is especially useful for the preparation of compounds in which R_1 is an alkyl group. The use of other organometallics, such as alkylzinc, -lithium, -tin or -aluminum reagents may also be useful when R_1 is an alkyl group (see references cited in Suzuki paper). Additional ways of coupling using a palladium catalysis and organoborane (A. Suzuki , Pure & Appl. Chem., 57, pgs. 1749-

1758, 1985), organozinc (R. Keenan et. al., Syn. Commun., 19, pgs.793-798, 1989), or organotin (J. K. Stille, Angew. Chem. Int. Ed., 25, pgs. 508-524, 1986) compounds may also be useful in this process step when R_1 is an aryl or olefinic group. Also potentially useful when R_1 is an alkyl, aryl, or olefinic group is the copper mediated coupling of aryl trifaltes, such as **7**, using the procedure of McMurry (J. E. McMurry et. al., Tett. Lett., 24, pgs. 2723-2726, 1983). The ketone **8** is converted to the hydroxylamine **9** by reaction with hydroxylamine, and subsequently reduced with borane in pyridine and hydrochloric acid. The hydroxylamine **9** is converted into the corresponding hydroxyurea **10** by the method outlined in Scheme I. The hydroxylamine **9** is also converted into the corresponding hydroxamate by the method outlined above for Scheme I.

Alternatively, the hydroxyureas of Formula (I) wherein R_4 is NR_5R_6 is a substituted amine or cyclic amine can be prepared by reaction of the appropriately substituted hydroxylamine hydrochloride of Formula (II) with phosgene to yield the acyl chloride intermediate which is reacted with the appropriate amine to yield the compounds of Formula (I).

An additional alternative to the use of phosgene is an alkyl chloroformate, such as ethyl chloroformate, in which case the resulting R_4 term of Formula (I) will determine the reaction time and temperature needed for the reaction to proceed, i.e. at O^{o} C or below or, if slow at an elevated temperatures of 100^{o}-200^{o} C in the appropriate solvent.

The preparation of the hydroxyureas of Formula (I) when -OB is a protecting group, as opposed to the free hydroxyl proceeds in a similiar manner. The protected hydroxylamine is reacted with phosgene or a phosgene equivalent, such as carbonyl diimidazole or phosgene trimer yielding a protected hydroxylamine intermediate which is reacted with an appropriate amine component (NHR_5R_6) to yield the protected hydroxyurea of Formula (I). Alternatively, the reaction of the protected hydroxylamine with trimethylsilyl isocyante or with sodium or potasium cyanate in an acidic solution as discussed above may be employed to prepare the protected hydroxyurea of Formula (I). This is followed by any means appropriate for the deprotection of the -OB group. Deprotection of the hydroxyl may be by hydrogenation with $H_2/Pd/C$ when B is benzyl , by mild acid treatment, such pyridinium para-toluenesulphonate in refluxing methanol or dilute HCl when B is tetrahydropyranyl , by a suitable base, such as potassium carbonate when B is an alkoyl or aroyl, by use of anhydrous fluoride $(R_4N^+)F^-$ when B is $Si(R_x)_3$, or by treatment with trifluoroacetic acid, trimethylsilyltrifilate with 2,6-lutidine, or anhydrous ether HCl when B is t-butyloxycarbonyl. In general, suitable protecting groups and methods for their removal will be found in T.W. Greene, Protective Groups in Organic Synthesis, Wiley, New York, 1981.

A hydroxylamine which is protected, such as O-benzylhydroxylamine or O-tetrahydropyranyl hydroxylamine, or other O-protected hydroxylamines can also be used to

produce the hydroxyureas of Formula (I) using as a starting material a compound having an active leaving group X (in structure **11**, Scheme III replace OH with X), such as Cl, Br, OMs, or OTs by reaction with the hydroxylamine (NH_2-OB) with heating in an appropriate solvent to yield a protected intermediate of Formula (II). The protected intermediate may then be deprotected using the standard removal conditions for the protecting group employed to yield the free hydroxylamines of Formula (II), or the protected intermediate may used as outlined above to prepare the O-protected hydroxyurea and then deprotected to yield the final compounds of Formula (I). Similarly, the above noted process can be used to make the starting amine compounds, chiral or not , as so desired, by use of NH_3, or N_3 and suitable reduction step, all well known to those skilled in the art.

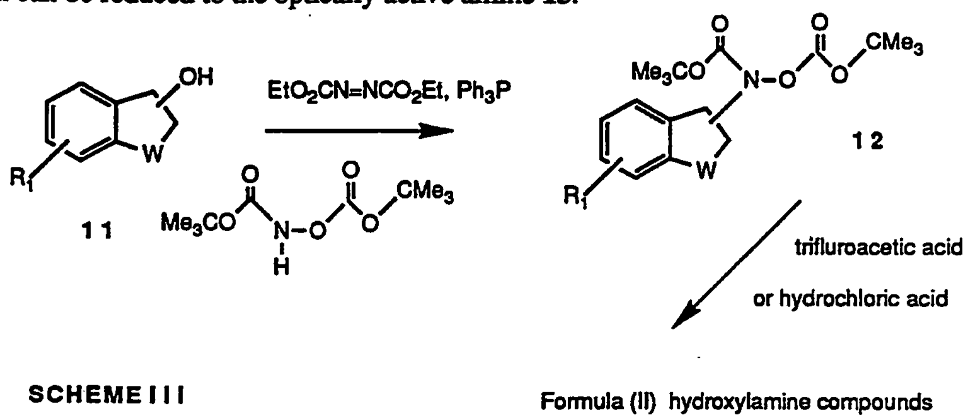
The starting compound, a halo compound can readily be prepared from the mesylate or toyslate derivatives (benzylic sulfonates are highly reactive and thus in most cases are used as non-isolated intermediates) or can be produced directly by a number of art known procedures from the corresponding alcohol. The mesylates or tosylate derivatives can be prepared from the ketone derivatives by reduction to the corresponding alcohol by any number of readily available agents, such as sodium borohydride, or lithium aluminum hydride. The alcohol is then reacted with mesyl or tosyl chloride in the presence of an appropriate base, for example pyridine or triethylamine, with or without additional solvent to form the mesylate or tosylate derivatives which are in turn displaced, for example either by in situ reaction or in a subsequent reaction with lithium chloride or bromide in acetone, to form the corresponding halogenated derivatives.

Selected examples of protected compounds of Formula (II) may also prepared by reaction of the alcohol **11** with a protected hydroxylamine, such as O-benzyl hydroxylamine or O-t-butyldiphenylsilyl hydroxylamine under solvolytic conditions, for example in the presence of trifluoroacetic acid. The protected intermediate may then be deprotected using the standard removal conditions for the protecting group employed to yield the free hydroxylamines of Formula (II), or the protected intermediate may be converted first to the protected urea and then to the final compounds of Formula (I) as discussed above.

Another synthetic pathway which will produce the hydroxylamines of Formula (II) and may also used to prepare the optically active intermediates, if the optically active alcohol derivative is used as a starting material is illustrated in Scheme III below. The alcoholic starting material **11** is treated with N,O-bis(t-butyloxycarbonyl)hydroxylamine and triphenylphosphine / diethyldiazodicarboxylate (DEAD) producing the intermediate **12** which is then treated with an appropriate acid, such as trifluroacetic acid or hydrochloric acid, to produce the free hydroxylamines of Formula (II). The optically active alcohol **11** may be prepared by enantioselective reduction of the corresponding ketone precursor with an appropriate reducing agent (M. Kawasaki et. al., Chem. Pharm. Bull., 33, pgs 52-60,

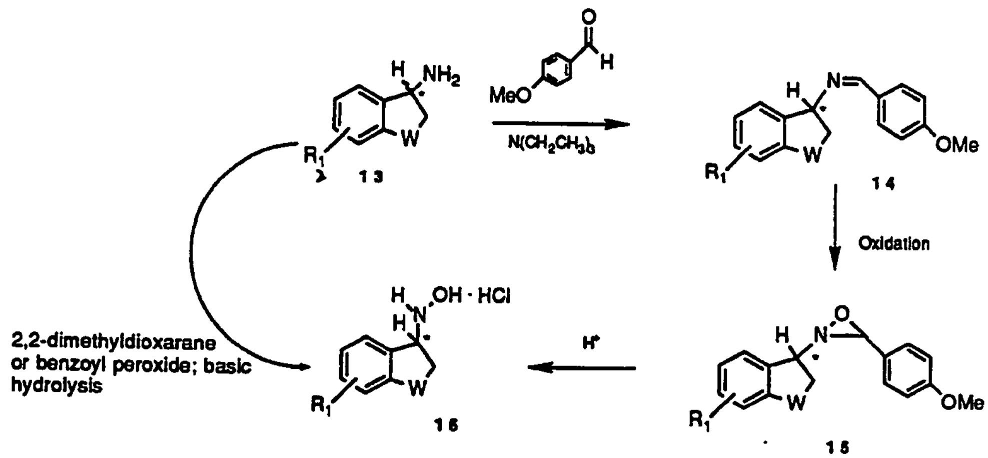
1985 or D. Mathre et. al., J. Org. Chem., 56, pgs 751-762 and references cited therein). The thus obtained optically active alcohol may also be converted to the corresponding optically active halo or sulfonate compound (see D. Mathre, compounds of Formula (II). Such steps as noted above are obviously useful as well to make the racemic mixture.

The alcoholic starting material **11** is treated with diphenylphosphoryl azide and triphenylphosphine / diethyldiazodicarboxylate (DEAD) producing the optically active azide which can be reduced to the optically active amine **13**.



SCHEME III

An additional route for preparation of the optically active compounds of Formula (I) is detailed in Scheme IV below. The sequence starts with optically active amines, obtained through a variety of methods including the classical methods of preparing salts with chiral acids, such as camphor sulfonic acids, such techniques being readily apparent to those skilled in the art. The requisite racemic amine can be prepared from the alcohol **11** or activated derivatives thereof, by the methods previously outlined above, substituting ammonia for (un)substituted hydroxylamines. One available review for resolving racemic compounds is by R.M. Secor, Chem. Rev., 63, 197 (1963). The starting material **13** is either the pure "R" or a pure "S" configuration which is then reacted to form the intermediate **14** with 4-methoxybenzaldehdye in triethylamine. The intermediate **14** is then oxidized by a variety of agents, such as MCPBA (metachloroperbenzoic acid), MPP (monoperoxyphthalate) or MMPP (magnesium monoperoxyphthalate) to yield the oxaziridine derivative **15** which under acidic conditions then yields the hydroxylamine salt **16**. The general procedure can be found in Polanski et al., Tetrahedron Letters., 28, 2453-2456 (1974). Alternatively, the optically active amine **13** may be converted directly to the chiral hydroxylamine **16** using dimethyldioxirane (Danishesky, et.al. J. Org. Chem., vol. 55, p1981-1983, 1990) or a peracid anhydride, such as benzoyl peroxide (R.M. Coates et.al., J. Org. Chem., vol. 55, 3464-3474, 1990).



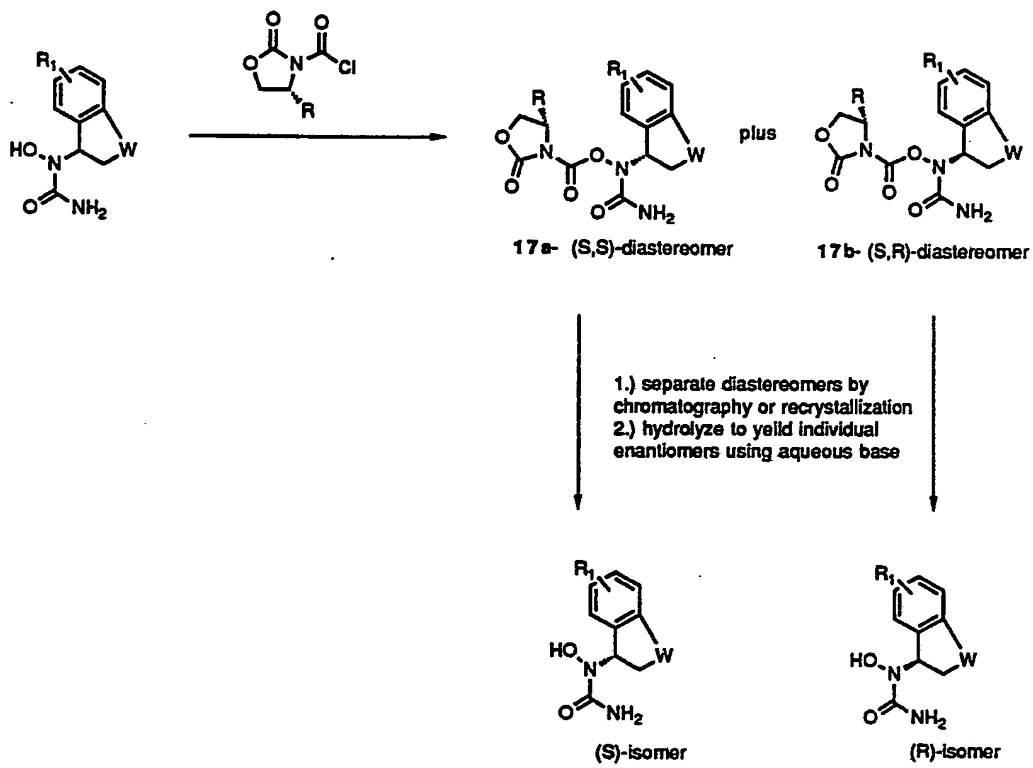
SCHEME IV

An additional method for obtaining the homochiral hydroxyureas of formula II is to form diastereomeric adducts of the racemic hydroxyureas or hydroxamates which may then be separated by a variety of commonly used techniques, including flash chromatography and HPLC. This approach is illustrated in Scheme V. Reaction with a homochiral oxazolidinone, for example 4-(phenylmethyl)-2-oxazolidinone (see Org. Syn., John Wiley & Sons, Inc., vol.68, p77 for preparation), with phosgene or a phosgene equivalent, such as phosgene trimer or carbonyl diimidazole, and a base in an anhydrous solvent, preferrably with NaH in toluene at reflux and then adding to this cooled solution at about -70°C to about 20 °C, preferably about -30 to about 0°C for use with phosgene. Should a phosgene equivalent be used to temperature range will be from about 20°C to about 200 °C. The thus formed intermediate, for eample, when phosgene is used, a chloro carbamate may be isolated.

Additional 4-substituted chiral oxazolidinones which may also be used are optionally substituted (R groups) aryl, arylmethyl, heteroaryl, or heteroarylmethyl wherein the substituents include, but are not limited to, mono or disubstituted alkyl, halo, alkoxy, cyano, or any other protected amino, alcohol, carboxy, or sulfur (regardless of oxidation state). Additionally R can be an alkyl moiety of greater than 2 carbons, preferably longer, such as t-butyl or isopropyl, which may be optionally substituted as well. Representative examples of the aryl and heteroaryl groups include, but not limited to phenyl, naphthyl, pyrrolyl, thienyl, thiazinyl and furanyl. These oxazolidinones are prepared from the chiral amino alcohols which are readily available from reduction of the chiral amino acids by the general procedure of Evans (Org. Syn., John Wiley & Sons, Inc. Vol. 68, p77 and references cited therein) which are incorporated by reference herein.

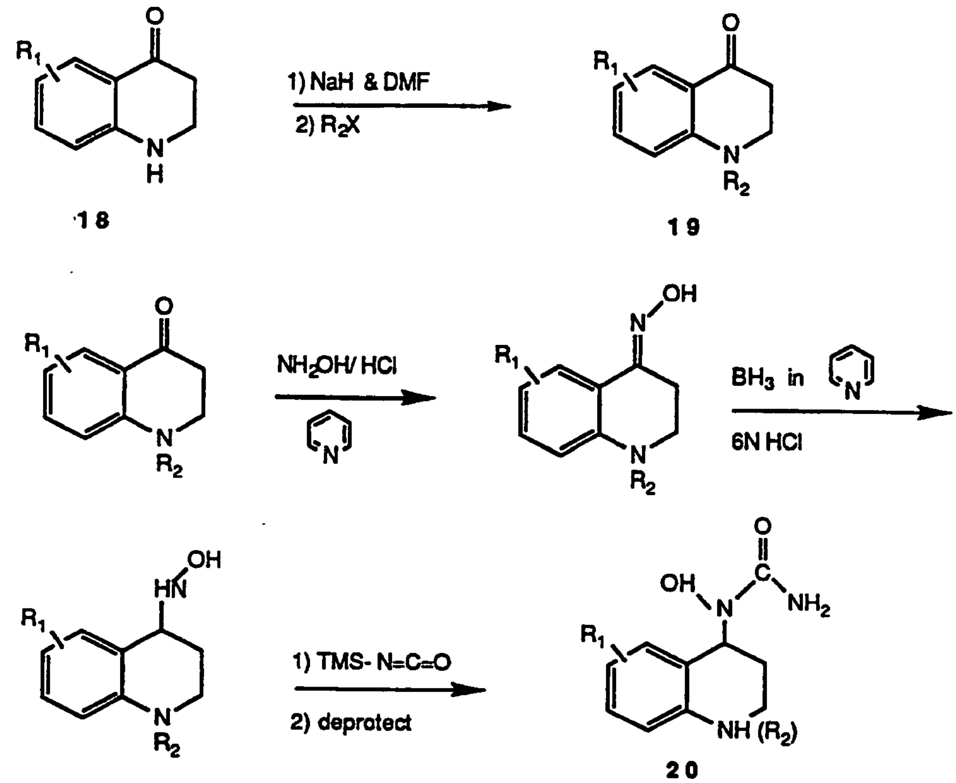
Addition of this adduct to a solution containing the hydroxyurea in a chloronated hydrocarbon or etheral solvent, preferably CH_2Cl_2, and a base (either an amine base such as trialkylamine or pyridine or a solid alkali metal carbonate, such as potassium or calcium, but most preferably triethylamine) affords the diastereomeric adducts, 17A and

17B. Chromatography or other physical methods are employed to separate these adducts which are then cleaved under basic conditions, for example using an alkali metal hydroperoxide, such as lithium, in an aqueous-etheral solvent (THF, glyme, digylme, ethyl ether) at about -20 to about 50°C, preferably from about -5°C to about room temperature, more preferably from about 0°C to about 15°C to yield the individual enantiomers of the hydroxyurea.



SCHEME V

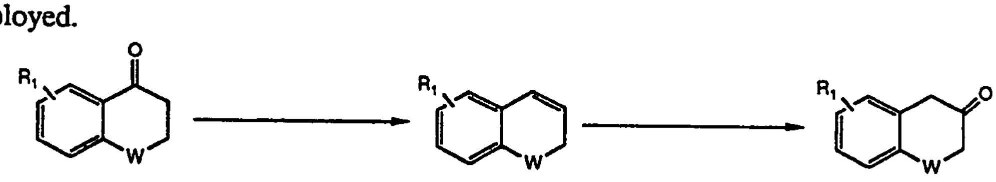
For the preparation of compounds in which W contains nitrogen a synthetic sequence similar to that outlined in Scheme I is employed (illustrated in Scheme VI). The starting materials **18** shown in Scheme VI can be prepared by the method of Kano et al (J.C.S. Perkin I, pgs 2105-2111, 1980 and references therein) or when R_1 = OMe by dealkylation/ refunctionalization as described in previous examples (Schemes I and II). When R_2 is alkyl or substituted alkyl, this group is attached by reaction of **18** using the appropriate base catalysis and alkylating reagent. When R_2 in the final product **20** is to be hydrogen, then protection of **18** by formation of the carbamate **19** is required ($R_2 = CO_2R_3$). Following transformation to the protected hydroxyurea **20**, the nitrogen is deprotected, for example with acid or fluoride when R_3 is t-butyl or trimethylsilylethyl respectively. Enantiomerically pure compounds can be prepared from **19** using the procedures outlined above (Schemes III and IV plus text) or from **20** (R_3 = alkyl or substituted alkyl or COR_3) by resolution (Scheme V).



R_2 = alkyl, substituted alkyl or CO_2R_3 where R_3 is t-butyl or trimethylsilylethyl

SCHEME VI

Compounds in which q= 0 and l = 1 (Formula (I)) can be prepared by the 1,2 carbonyl transposition of the ketone intermediates used to prepare compounds in which q= 1 and l = 0 (Scheme VII). Many such 1,2 carbonyl transposition procedures are known (see Tetrahedron, 39, p345, 1983 for review). A particularly useful and general procedure is the reduction, dehydration, hydroboration-oxidation sequence (see Kirkiacharian, B.S.et. al., Synthesis, p815, 1990 for hydroboration-oxidation). When W contains nitrogen, suitable protection is required to effect this transformation. Protecting groups such as those previously outlined are applicable. When W is sulfur the oxidation of the borane to the ketone may afford sulfur oxidation products, sulfoxide or sulphones. In cases where selective reduction of the oxidized sulfur is not possible alternative routes are employed.



Scheme VII

Pharmaceutically acceptable base addition salts and their preparation are well known to those skilled in pharmaceuticals. Pharmaceutically acceptable bases (cations) of the compounds of Formula (I) which are useful in the present invention include, but are not limited to nontoxic organic and inorganic bases, such as ammonium hydroxide, arginine, organic amines such as triethylamine, butylamine, piperazine and (trihydroxy)methylamine, nontoxic alkali metal and alkaline earth metal bases, such as potassium, sodium and calcium hydroxides. Pharmaceutically acceptable acid addition salts of the compounds of Formula (I) which are useful in the present invention include, but are not limited to, maleate, fumarate, lactate, oxalate, methanesulfonate, ethane-sulfonate, benzenesulfonate, tartrate, citrate, hydrochloride, hydrobromide, sulfate and phosphate salts and such salts can be readily repared by known techniques to those skilled in the art.

METHOD OF TREATMENT

It has now been discovered that the compounds of Formula (I) are useful for treating disease states mediated by the 5-lipoxygenase pathway of arachidonic acid metabolism in an animal, including mammals, in need thereof. The discovery that the compounds of Formula (I) are inhibitors of the 5-lipoxygenase pathway is based on the effects of the compounds of Formula (I) on the production of 5-lipoxygenase products in blood *ex vivo* and on the 5-lipoxygenase *in vitro* assays, some of which are described hereinafter. The 5-lipoxygenase pathway inhibitory action of the compounds of Formula (I) was confirmed by showing that they impaired the production of 5-lipoxygenase products such as leukotriene B_4 production by RBL-1 cell supernatants. It has also been found, unexpectedly that the compounds of Formula (I) possess analgesic activity, using the phenylbenzoquinone writhing test. It has further been found that the compounds of Formula (I) do not appear to inhibit prostaglandin production *in vitro* and are therefore selective 5-lipoxygenase inhibitors. Test data presented in this specification is consistent with the premise that the mechanism of analgesic activity of the compounds of this invention is distinct and independent of the mechanism of action commonly associated with cyclooxygenase inhibitors.

The pathophysiological role of arachidonic acid metabolites has been the focus of recent intensive studies. In addition to the well-described phlogistic activity (i.e. general inflammatory activity) of prostaglandins, the more recent description of similar activity for other eicosanoids, including the leukotrienes, has broadened the interest in these products as mediators of inflammation [See, O'Flaherty, Lab. Invest., 47, 314-329 (1982)]. The reported discovery of potent chemotactic and algesic activity for LTB_4 [see, Smith, Gen. Pharmacol., 12, 211-216 (1981) and Levine et al., Science, 225, 743-745 (1984)], together with known LTC_4 and LTD_4-mediated increase in capillary permeability [see, Simmons et al., Biochem. Pharmacol., 32, 1353-1359 (1983), Vane et al., Prostaglandins, 21, 637-647 (1981), and Camp et al., Br. J. Pharmacol., 80, 497-502

(1983)], has led to their consideration as targets for pharmacological intervention in both the fluid and cellular phases of inflammatory diseases.

The pharmacology of several inflammatory model systems has attested to the effectiveness of corticosteroids in reducing the cellular infiltration. These results, and the observation that corticosteroids inhibit the generation of both cyclooxygenase and lipoxygenase products, suggest that such dual inhibitors may effectively reduce both the fluid and cellular phases of the inflammatory response since selective cyclooxygenase inhibitors do not reliably inhibit cell influx into inflammatory sites [See, Vinegar et al., Fed. Proc., 35, 2447-2456 (1976), Higgs et al., Brit. Bull., 39, 265-270 (1983), and Higgs et al., Prostaglandins, Leukotrienes and Medicine, 13, 89-92 (1984)]. Under optimal conditions, it is likely that an agent with preferential lipoxygenase inhibitory activity would not share the ulcerogenic liability of cyclooxygenase inhibitors or the toxicity of corticosteroids. This may suggest that the compounds of the present invention could be useful in treating diseases, such as osteoarthritis, where it is beneficial to limit ulcerogenic activity or steroidal side effects. [See Palmoski et al., "Benoxaprofen Stimulates Proteoglycan Synthesis in Normal Canine Knee Cartiledge in Vitro," Arthritis and Rheumatism 26, 771-774 (1983) and Rainsford, K.D., Agents and Actions 21, 316-319 (1987).]

Clinical data supports the enthusiasm for inhibitors of the 5-lipoxygenase pathway in a variety of inflammatory diseases in which granulocyte and/or monocyte infiltration is prominent. The reported demonstration of elevated levels of LTB_4 in rheumatoid arthritic joint fluid [See, Davidson et al., Ann. Rheum. Dis., 42, 677-679 (1983)] also suggests a contributing role for arachidonic acid metabolites in rheumatoid arthritis. Sulfasalazine, which is used for treatment of ulcerative colitis, has been reported to inhibit LTB_4 and 5-HETE production in vitro [See, Stenson et al., J. Clin. Invest., 69, 494-497 (1982)]. The recently reported preliminary observation of efficacy, including remission, reported with sulfasalazine treatment of rheumatoid arthritic patients [See Neumann et al., Brit. Med. J., 287, 1099-1102 (1983)] illustrates the utility of inhibitors of the 5-lipoxygenase pathway in rheumatoid arthritis.

Additionally it has been reported that inflamed gastrointestinal mucosa from inflammatory bowel disease patients showed increased production of LTB_4 [See, Sharon et al., Gastroenterol., 84, 1306 (1983)], which suggests that sulfasalazine can be effective by virtue of inhibition of production of chemotactic eicosanoids (such as the 5-lipoxygenase pathway product known as LTB_4). The observations serve to underscore utility of inhibitors of the 5-lipoxygenase pathway in inflammatory bowel disease.

Another area of utility for an inhibitor of the 5-lipoxygenase pathway is in the treatment of psoriasis. It was demonstrated that involved psoriatic skin had elevated levels of LTB_4 [See, Brain et al., Lancet, 19, February 19, 1983]. The promising effect of

benoxaprofen on psoriasis [See, Allen et al., Brit. J. Dermatol., 109, 126-129 (1983)], a compound with in vitro lipoxygenase inhibitory activity lends support to the concept that inhibitors of the 5-lipoxygenase pathway can be useful in the treatment of psoriasis.

Lipoxygenase products have been identified in exudate fluids from gouty patients. This disorder is characterized by massive neutrophil infiltration during the acute inflammatory phases of the disease. Since a major 5-lipoxygenase product, LTB_4, is produced by neutrophils, it follows that inhibition of the synthesis of LTB_4 may block an amplification mechanism in gout.

Another area in which inhibitors of the 5-lipoxygenase product can have utility is in myocardial infarction. Studies in dogs with the dual inhibitor, BW755-C, demonstrated that the area of infarction following coronary occlusion was reduced, and such reduction was attributed to inhibition of leukocyte infiltration into the ischaemic tissue [See, Mullane et al., J. Pharmacol. Exp. Therap., 228, 510-522 (1984)].

Yet another area in which inhibitors of lipid peroxidation involved in the OPUFA mediated can have utility is that generally refered as degenerative neurological disorders, such as Parkinson's disease. Another area is that of traumatic or ischemic injuries, such as stroke, brain or spinal cord injuries and inflammatory disease of the brain and spinal column. More specicially preferred disease states are the mycardial induced ischemic injuries and/or reperfusion injuries. [See, Braughler et al., Jour. Biol. Chem., Vol. 262, No. 22, pp10438-40 (1987), see also Xu et al., J. Neurochemistry, 55, 907-912 (1990); Asano et al., Molecular and Chemical Neuropathology, 10:101-133 (1989) and Bracken et al., NE. J. Med., 322:1405-1411 (1990)]

Yet another area of utility for inhibitors of the 5-lipoxygenase pathway is in the area of prevention of rejection of organ transplants. [See, e.g., Foegh et al., Adv. Prostaglandin, Thromboxane, and Leukotriene Research, 13, 209-217 (1983).]

Yet another utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of tissue trauma. [See, e.g., Denzlinger et al. Science, 230 (4723), 330-332 (1985)].

Furthermore, another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of inflammatory reaction in the central nervous system, including multiple sclerosis. [See, e.g., Mackay et al., Clin. Exp. Immunology, 15, 471-482 (1973)].

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of asthma. [See, e.g., Ford-Hutchinson, J. Allergy Clin. Immunol., 74, 437-440 (1984)]. Additionally another utility for inhibitors of the 5-lipoxygense pathway is in the treatment of Adult Respitory Distress Syndrome. [See, e.g., Pacitti et. al., Circ. Shock, 21, 155-168 (1987)]. Yet another utility for inhibitors of the 5-lipoxygenase pathway is in the treament of allergic rhinitis.

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of vasculitis, glomerulonephritis, and immune complex disease. [See Kadison et al., "Vasculitis: Mechanism of Vessel Damage" in Inflammation: Basic Principles and Clinical Correlates, 703-718, Ed. Gallin et al., Raven Press, N.Y., N.Y. (1988).]

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of dermatitis. [See Pye et al., "Systemic Therapy" in Textbook of Dermatology, Vol. III, 2501-2528, Ed. Rook et al., Blackwell Scientific Publications, Oxford, England (1986).]

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of atherosclerosis. Recent studies have shown that inhibition of oxidative modification of low density lipoprotein slows progression of atherosclerosis, and that inhibitors of lipoxygenase effectively inhibit cell-induced oxidative modification. [See Carew et al., Proc. Natl. Acad. Sci. USA, 84, 7725-7729, November 1987; and Steinberg, D., Cholesterol and Cardiovascular Disease, 76, 3, 508-514 (1987).]

An additional area of utility for inhibitors of the 5-lipoxygenase pathway is in the opthamalogic area, in particular general inflammation of the corneal anterior and posterior segments due to disease or surgery such as in post surgical inflammation, uveitis, and allergic conjuntivitis. [See Rao N. et al. Arch. Ophathmal. 105 (3) 413-419 (1987); Chiou, L. and Chiou, G. J. Ocular Pharmacol. 1, 383-390 (1985); Bazan H., J. Ocular Pharma. 4, 43-49 (1988); and Verbey N.L. et al., Current Eye Research 7, 361-368 (1988).]

FORMULATION OF PHARMACEUTICAL COMPOSITIONS

The pharmaceutically effective compounds of this invention are administered in conventional dosage forms prepared by combining a compound of Formula (I) or (II) ("active ingredient") in an amount sufficient to produce 5-lipoxygenase pathway inhibiting activity with standard pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary

widely but preferably will be from about 25 mg. to about 1 g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

Preferably, each parenteral dosage unit will contain the active ingredient [i.e., the compound of Formula (I)] in an amount of from about 30 mg. to about 300 mg. Preferably, each oral dosage will contain the active ingredient in an amount of from about 50 mg to about 1000 mg.

The compounds of Formula (I) may also be administered topically to a mammal in need of the inhibition of the 5-lipoxygenase pathway of arachidonic acid metabolism. Thus, the compounds of Formula (I) may be administered topically in the treatment or prophylaxis of inflammation in an animal, including man and other mammals, and may be used in the relief or prophylaxis of 5-lipoxygenase pathway mediated diseases such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

The amount of a compound of Formula (I) (hereinafter referred to as the active ingredient) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the inflammatory condition and the animal undergoing treatment, and is ultimately at the discretion of the physician. A suitable anti-inflammatory dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of a compound of Formula (I) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

.The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be

'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as: liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic sulfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The compounds of Formula (I) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler,

may be prepared by conventional techniques. The daily dosage amount of a compound of Formula (I) administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

This invention relates to a method of treating a disease state which is mediated by the 5-lipoxygenase pathway in an animal in need thereof, including humans and other mammals, which comprises administering to such animal an effective, 5-lipoxygenase pathway inhibiting amount of a Formula (I) compound. This invention further relates to a method of treating analgesia in an animal in need thereof, which comprisies administering to such animal an effective, analgesia inhibiting amount of a compound of Formula (I).

By the term "treating" is meant either prophylactic or therapeutic therapy. By the term "mediated" is meant caused by or exacerbated by. Such Formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the Formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The Formula (I) compound is administered to an animal in need of inhibition of the 5-lipoxygenase pathway in an amount sufficient to inhibit the 5-lipoxygenase pathway. The route of administration may be oral, parenteral, by inhalation or topical.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day for both 5-lipoxygenase and algesia treatment.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a Formula (I) or (II) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular animal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the Formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following

examples further illustrate the synthesis and use of the compounds of this invention. The following examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

SYNTHESIS EXAMPLES

Example 1

N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

a) 6-Hydroxy-1-tetralone To a solution of ethanethiol (17 mL, 230 mmol) in dry DMF (150 mL) was added slowly NaH (4.5 g of 80% suspension in mineral oil, 150 mmol). When the evolution of gas subsided, 6-methoxy-1-tetralone (10 g, 56.8 mmol) was added. The resulting mixture was heated at 150°C for 3 h, then allowed to cool and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed successively with 3N HCl, H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the crude product (9.2 g, 100%) was used without further purification.
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.98 (d, 1H); 6.78 (dd, 1H); 6.72 (d, 1H); 2.91 (t, 2H); 2.64 (t, 2H); 2.12 (m, 2H).

b) 6-Benzyloxy-1-tetralone To a solution of 6-hydroxy-1-tetralone (9.2 g, 56.8 mmol) in DMF (150 mL) was added potassium hydride (2.49 g, 62 mmol). When the evolution of gas subsided, benzyl bromide (10.6 g, 62 mmol) was added. After stirring for 2 h at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed successively with 3N HCl, H_2O and saturated aqueous NaCl. Removal of the solvent in vacuo and purification by flash chromatography eluting with a gradient of 0 - 100% CH_2Cl_2/ hexanes yielded the desired product (9.7 g, 73%). The infrared spectrum of the product indicated a conjugated ketone at 1665 - 1685 cm^{-1}. The NMR spectrum indicated the presence of the benzyl methylene at δ 5 and aromatic benzyl protons at δ 7.4.

c) 6-Benzyloxy-1-tetralone oxime To a solution of 6-benzyloxy-1-tetralone (9.7 g, 38 mmol) in dry pyridine (100 mL) was added hydroxylamine hydrochloride (5.3 g, 76 mmol). The resulting mixture was heated at 50°C for 30 min, then was allowed to cool and concentrated under reduced pressure. The residue was crystallized from ethanol to yield the desired oxime (7.3 g, 71%).

d) N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine. To a solution of the oxime prepared above (4.7 g, 17.6 mmol) in 2:1 Et_2O: MeOH (400 mL) at 0°C was added BH_3·pyridine complex (7.8 mL, 77 mmol). After warming to room temperature and

stirring for 1 h, 6N HCl (10 mL) was added, and the reaction mixture was stirred an additional 2 h. Thin layer analysis indicated that the reaction was incomplete, so additional BH_3·pyridine (2 mL, 20 mmol) was added, and the mixture was stirred for 3 h. At this time, more BH_3·pyridine (2 mL, 20 mmol) was added, followed by 6N HCl (30 mL), and the reaction was allowed to stir overnight. The reaction mixture was adjusted to pH 10 with 10% NaOH and extracted with Et_2O. The organic extract was washed successively with H_2O and saturated aqueous NaCl and concentrated *in vacuo* to yield the hydroxyamine (4.3 g, 92%), which was used without further purification.

e) N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)]-N-hydroxyurea To a solution of the hydroxyamine prepared above (4.3 g, 15.9 mmol) in dry THF (120 mL) was added trimethylsilyl isocyanate (4.3 mL, 31.8 mmol). After heating at 60°C for 1 h, the reaction mixture was concentrated in vacuo. The residue was dissolved in EtOAc, washed successively with H_2O, saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent under reduced pressure and trituration with Et_2O (60 mL) provided the desired hydroxyurea (4.0 g, 87%); m.p. 160 - 162°C.
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.36 (m, 5H); 7.20 (d, 1H); 6.80 (dd, 1H); 6.70 (d, 1H); 5.45 (br t, 1H); 5.04 (s, 2H); 2.71 (m, 2H); 2.00 (m, 3H); 1.75 (m, 1H).
CIMS (isobutane); m/e (rel. int.) : 313 [$(M+H)^+$,2), 252 (19), 238 (17), 237 (100).
Anal., calc. for $C_{18}H_{20}N_2O_3$: C 69.23, H 6.41, N 8.97; found: C 69.19, H 6.46, N 9.03.

Example 2

N-1-(5-Benzyloxyindanyl)-N-hydroxyurea

a) 5-Hydroxy-1-indanone. To a solution of ethanethiol (35 mL, 0.473 mol) in dry DMF (300 mL) under an argon atmosphere was added slowly sodium hydride (8.47 g of 80% suspension in mineral oil, 0.308 mol). After the evolution of hydrogen ceased, 5-methoxy-1-indanone (20.0 g, 0.123 mol) was added, and the resulting mixture was heated at 135°C. After heating for 1 1/2 h, thin layer chromatographic analysis indicated that the reaction was complete, and excess ethanethiol was removed by distillation at atmospheric pressure. The reaction was then concentrated under reduced pressure. The residue was dissolved in EtOAc and extracted with 1 : 1 10% HCl/ saturated aqueous NaCl (500 mL). The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The mixture was filtered and allowed to stand at 0°C for several d. The solid which formed was collected by filtration and washed with 1 : 1 EtOAc/ hexanes to afford the title compound as a crystalline solid (12.44 g, 68%).

b) 5-Benzyloxy-1-indanone. To a solution of 5-hydroxy-1-indanone (8.02 g, 54.2 mmol) in dry DMF (120 mL) under an argon atmosphere was added slowly sodium hydride (1.64 g of 80% suspension in mineral oil, 59.6 mmol). After the evolution of hydrogen ceased, benzyl chloride (7.12 mL, 60.0 mmol) was added, and the resulting mixture was stirred for 15 min. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between EtOAc and 1: 1 saturated aqueous NaCl/ 3 N HCl. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was used without further purification.

c) 5-Benzyloxy-1-indanone oxime. To a solution of 5-benzyloxy-1-indanone, prepared above, in dry pyridine (100 mL) was added hydroxylamine hydrochloride (7.7 g, 110 mmol). The resulting mixture was heated at 60°C for 1 h. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH/ H_2O to provide the desired oxime as an off-white powder (10.43 g, 76% for two steps).

d) N-1-(5-Benzyloxyindanyl)-N-hydroxyamine. To a solution of 5-benzyloxy-1-indanone oxime (7.5 g, 29.6 mmol) in 2 : 1 THF/ EtOH (360 mL) at 5°C was added BH_3·pyridine (15 mL, 149 mmol), maintaining the temperature at 5 - 8°C. To the resulting mixture was added 3 N HCl (150 mL) dropwise over 20 min. The resulting mixture was allowed to warm to room temperature and stand overnight. Ether (500 mL) was added, followed by solid Na_2CO_3 and the mixture was poured into a mixture of 2N NaOH and saturated aqueous NaCl. The layers were separated, and the organic phase was dried (K_2CO_3). The solvent was removed *in vacuo*, and the solid residue was dissolved in CH_2Cl_2 (40 mL). The mixture was concentrated on a steam bath, and Et_2O (50 - 100 mL) was added. This was further concentrated and hexanes (50 mL) were added, followed by a seed crystal. The mixture was allowed to cool, and the solid which formed was collected by filtration and dried *in vacuo* to afford the title compound (4.55 g, 60%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.40 (m, 6H); 6.83 (m, 2H); 5.52 (br s, 2H); 5.05 (s, 2H); 4.50 (dd, 1H); 3.02 (m, 1H); 2.83 (m, 1H); 2.30 (m, 1H); 2.14 (m, 1H).

e) N-1-(5-Benzyloxyindanyl)-N-hydroxyurea. To a solution of N-1-(5-benzyloxyindanyl)-N-hydroxyamine (4.55 g, 17.8 mmol) in dry THF (100 mL) under an argon atmosphere was added trimethylsilyl isocyanate (5 mL, 32 mmol). The resulting mixture was heated at reflux for 4.5 h, then allowed to cool to room temperature and stand overnight. The solvent was removed under reduced pressure, and the solid residue was recrystallized from MeOH/ $CHCl_3$ to afford a white crystalline solid (2.5 g). The mother liquor was purified by flash chromatography, eluting with a solvent gradient of 5 - 10 % MeOH/ $CHCl_3$. The combined

solid material was further recrystallized from EtOH, washed with Et_2O and dried under reduced pressure to afford the title compound (2.62 g, 49%). m.p. 167°C (dec)
Anal. Calc. for $C_{17}H_{18}N_2O_3$: C 68.44, H 6.08, N 9.39; found C 68.64, H 6.39, N 9.42.
250 MHz ^{1}H NMR ($CDCl_3$/ MeOH-d_4) : δ 7.46 - 7.16 (m, 6H); 6.82 (m, 2H); 5.78 (dd, 1H); 5.04 (s, 2H); 3.03 (m, 1H); 2.84 (m, 1H); 2.45 - 2.13 (m, 2H).

Example 3

N-1-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

a) 6-Methoxy-1-tetralone oxime To a solution of 6-methoxy-1-tetralone (5.19 g, 29.0 mmol) in dry pyridine (50 mL) was added hydroxylamine hydrochloride (4.41 g, 58.0 mmol). The resulting mixture was heated at 50°C for 40 min and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH/ H_2O to provide 5.08 g of the oxime (92% yield).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.82 (d, 1H); 6.76 (dd, 1H); 6.66 (d, 1H); 3.80 (s, 3H); 2.78 (t, 2H); 2.73 (t, 2H); 1.85 (m, 2H).

b) N-1-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine To a solution of 6-methoxy-1-tetralone oxime (568 mg, 2.96 mmol) in 1 : 2 MeOH/ Et_2O (5 mL), was added BH_3·pyridine (0.9 mL, 9.0 mmol), followed by the dropwise addition of 3 N HCl. The resulting mixture was stirred at room temperature for 1 h, and additional BH_3·pyridine (0.25 mL, 2.5 mmol) was added followed by the dropwise addition of 3 N HCl. After stirring at room temperature for 5 h, sodium carbonate was added, and the mixture was extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*. The residue was dissolved in ethanol, and 3 N HCl was added dropwise with cooling. Sodium carbonate was added, and the mixture was extracted with Et_2O. The organic extract was washed with H_2O and saturated aqueous NaCl. Removal of the solvent *in vacuo* provided a white solid (391 mg, 69% yield) which was used without further purification.

c) N-1-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea
To a solution of N-1-(6-methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine (339 mg, 1.76 mmol) in THF (5 mL) was added trimethylsilyl isocyanate (0.40 mL, 2.96 mmol). The resulting mixture was heated to 60°C for 1-1/2 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with

Et_2O (10 mL) and recrystallized with CH_2Cl_2 to provide a white crystalline solid (149 mg, 39% yield). m.p. 164 ^oC.

250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.25 (d, 1H); 6.76 (dd, 1H); 6.65 (d, 1H); 5.50 (br t, 1H); 5.37 (br s, 1H); 5.24 (br s, 2H); 3.78 (s, 3H); 2.77 (m, 2H); 2.05 (m, 3H); 1.78 (m, 1H).

IR (cm^{-1}) : 3470, 3320, 3180, 2940, 2900, 1650.

CIMS / NH_3 (m/e, rel. int.) : 237 ($M+H^+$, 12); 221 (9); 176 (16); 161 (100).

Anal. Calc. for $C_{12}H_{16}N_2O_3$: C 61.00, H 6.83, N 11.86; found C 60.21, H 6.77, N 11.72.

Example 4

N-1-(1,2,3,4-Tetrahydronaphthyl)-N-hydroxyurea

a) 1-Tetralone oxime To a solution of 1-tetralone (4.97 g, 34.0 mmol) in dry pyridine (30 mL) was added hydroxylamine hydrochloride (3.62g, 52.0 mmol). The resulting mixture was heated at 50^{o}C for 1 h and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from ethanol to provide 5.42 g of the oxime (99% yield).

250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.90 (br d, 1H); 7.21 (m, 3H); 2.80 (t, 2H); 2.75 (t, 2H); 1.90 (m, 2H); 1.65 (br, 1H).

b) N-1-(1,2,3,4-Tetrahydronaphthyl)-N-hydroxyamine To a solution of 1-tetralone oxime (488 mg, 3.0 mmol) in CH_2Cl_2 (5 mL) was added BH_3·pyridine (0.9 mL, 9.0 mmol) followed by glacial acetic acid (3 mL). The resulting mixture was heated to reflux for 4 h, and the solvent was removed *in vacuo*. The residue was treated with 3N HCl (20 mL) and stirred overnight. Sodium carbonate was added and the mixture extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl. Removal of the solvent *in vacuo* provided a white solid (368 mg, 77% yield).

c) N-1-(1,2,3,4-Tetrahydronaphthyl)-N-hydroxyurea To a solution of N-1-(1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine (313 mg, 1.9 mmol) in THF (5 mL) was added trimethylsilyl isocyanate (0.31 mL, 2.3 mmol). The resulting mixture was heated to 60^{o}C for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O (5 mL) and recrystallized with CH_2Cl_2 to provide a white crystalline solid (154 mg, 39% yield). m.p. 168 - 169^{o}C.

250 MHz ^{1}H NMR ($CDCl_3$/ MeOD) : δ 7.25 (m, 4H); 5.53 (br t, 1H); 2.84 (m, 2H); 2.10 (m, 3H), 1.86 (m, 1H).

IR (cm^{-1}) : 3470, 3320, 3200, 2920, 1660.

CIMS / CH_4 (m/e, rel. int.) : 207 ($M+H^+$, 7); 146 (22); 131 (100).
Anal. Calc. for $C_{11}H_{14}N_2O_2 \cdot 1/8\ H_2O$: C 63.37, H 6.89, N 13.44; found C 63.37, H 6.75, N 13.39.

Example 5
N-1-[6-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea

a) 6-(4-Methoxybenzyloxy)-1-tetralone To a solution of 6-hydroxy-1-tetralone (see example 1; 3.05 g, 18.8 mmol) in DMF (30 mL) was added sodium hydride (0.60 g of 80% suspension in mineral oil, 18.8 mmol). After the evolution of hydrogen, 4-methoxybenzyl chloride (2.84 g, 20.0 mmol) was added, and the resulting mixture was heated at 50°C for 1 h, followed by heating at 90°C for 1 h. The reaction mixture was allowed to cool and was concentrated under reduced pressure. The residue was partitioned between EtOAc and 3 N HCl, and the organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with CH_2Cl_2 to provide 4.13 g (78% yield) of the desired product.
250 MHz ^{1}H NMR ($CDCl_3$) : δ 8.00 (d, 1H); 7.34 (d, 2H); 6.98 - 6.86 (m, 3H); 6.78 (d, 1H); 5.04 (s, 2H); 3.82 (s, 3H); 2.92 (t, 2H); 2.63 (t, 2H); 2.12 (m, 2H).

b) 6-(4-Methoxybenzyloxy)-1-tetralone oxime To a solution of 6-(4-methoxybenzyloxy)-1-tetralone (469 mg, 1.7 mmol) in dry pyridine (4 mL) was added hydroxylamine hydrochloride (0.27 g, 3.9 mmol). The resulting mixture was heated at 50°C for 1 h and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH to provide 440 mg of the oxime (87% yield).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.82 (d, 1H); 7.35 (d, 2H); 6.91 (d, 2H); 6.82 (dd, 1H); 6.72 (d, 1H); 5.00 (s, 2H); 3.82 (s, 3H); 2.80 (t, 2H); 2.74 (t, 2H); 1.86 (m, 2H); 1.64 (br s, 1H).

c) N-1-[6-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine To a solution of 6-(4-methoxybenzyloxy)-1-tetralone oxime (713 mg, 2.4 mmol) in 1 : 2 EtOH/ THF (20 mL) was added $BH_3 \cdot$pyridine (0.48 mL, 4.8 mmol). The resulting mixture was stirred at room temperature for 2 h, at which time 3N HCl was added dropwise. The reaction mixture was stirred at room temperature overnight. Sodium carbonate was added and the mixture extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent *in vacuo* provided a white solid (489 mg, 68% yield).

d) N-1-[6-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea To a solution of N-1-[6-(4-methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine (160 mg, 0.54 mmol) in THF (8 mL) was added trimethylsilyl isocyanate (0.16 mL, 1.2 mmol). The resulting mixture was heated at 60°C for 2 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O and purified by flash chromatography, eluting with CH_2Cl_2. Recrystallization from CH_2Cl_2 provided 65 mg (35% yield) of the hydroxyurea. m.p. 165 - 166°C.
250 MHz ^{1}H NMR ($CDCl_3$/ MeOH-d_4) : δ 7.32 (d, 2H); 7.19 (d, 1H); 6.90 (d, 2H); 6.80 (dd, 1H); 6.71 (d, 1H); 5.45 (br t, 1H); 4.96 (s, 1H); 3.83 (s, 3H); 2.73 (m, 2H); 2.03 (m, 3H); 1.78 (m, 1H).
IR (cm^{-1}) : 3480, 3240, 2930, 1660, 1645.
CIMS/ NH_3 (m/e, rel. int.) : 342 (M+H$^+$, 2); 282 (45); 267 (100); 147 (20); 121 (50).
Anal. Calc. for $C_{19}H_{22}N_2O_4 \cdot 1/4\ H_2O$: C 65.79, H 6.54, N 8.08; found C 65.89, H 6.41, N 8.07.

Example 6

N-1-[6-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea

a) 6-(4-Chlorobenzyloxy)-1-tetralone To a solution of 6-hydroxy-1-tetralone (see example 1, 489 mg, 3.0 mmol) in DMF (10 mL) was added sodium hydride (105 mg of 80% suspension in mineral oil, 3.5 mmol). After the evolution of hydrogen, 4-chlorobenzyl chloride (576 mg, 3.6 mmol) was added, and the resulting mixture was stirred at room temperature for 2 h, followed by heating at 60°C for 2 h. The reaction mixture was allowed to cool and was concentrated under reduced pressure. The residue was partitioned between EtOAc and 3 N HCl, and the organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with CH_2Cl_2 to provide 600 mg (70% yield) of the desired product.
250 MHz ^{1}H NMR ($CDCl_3$) : δ 8.01 (d, 1H); 7.35 (s, 4H); 6.90 (dd, 1H); 6.80 (d, 1H); 5.09 (s, 2H); 2.91 (t, 2H); 2.64 (t, 2H); 2.13 (m, 2H).

b) 6-(4-Chlorobenzyloxy)-1-tetralone oxime To a solution of 6-(4-chlorobenzyloxy)-1-tetralone (286 mg, 1.0 mmol) in dry pyridine (3 mL) was added hydroxylamine hydrochloride (140 mg, 2.0 mmol). The resulting mixture was heated at 50°C for 30 min and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from ethanol to provide 248 mg of the oxime (81% yield).

250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.84 (d, 1H); 7.36 (s, 4H); 6.82 (dd, 1H); 6.72 (d, 1H); 5.04 (s, 2H); 2.80 (t, 2H); 2.73 (t, 2H); 1.88 (m, 2H), 1.65 (br, 1H).

c) N-1-[6-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine To a solution of 6-(4-chlorobenzyloxy)-1-tetralone oxime (2.20 g, 7.31 mmol) in 1 : 2 EtOH/ THF (15 mL) was added BH_3·pyridine (1.46 mL, 14.6 mmol). The resulting mixture was stirred at room temperature for 1 h, at which time 3N HCl (50 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h. Sodium carbonate was added and the mixture extracted with CH_2Cl_2 (3x). The organic extract was washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent *in vacuo* provided the desired hydroxyamine (2.02 g, 91% yield).

d) N-1-[6-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea To a solution of N-1-[6-(4-chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine (180 mg, 0.60 mmol) in THF (3 mL) was added trimethylsilyl isocyanate (0.16 mL, 1.2 mmol). The resulting mixture was heated at 60°C for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O and recrystallized from CH_2Cl_2 to provide 71 mg (34% yield) of the hydroxyurea. m.p. 166°C.
250 MHz ^{1}H NMR ($CDCl_3$/ MeOH-d_4) : δ 7.36 (s, 4H); 7.20 (d, 1H); 6.78 (dd, 1H); 6.70 (d, 1H); 5.43 (br t, 1H); 5.00 (s, 2H); 2.74 (m, 2H); 2.00 (m, 3H); 1.77 (m, 1H).
IR (cm^{-1}) : 3460, 3320 - 3100, 2920, 2860, 1640.
CIMS / NH_3 (m/e, rel. int.) : 347 ($M+H^+$, 10); 331 (17); 286 (52); 271 (100).
Anal. Calc. for $C_{18}H_{19}N_2O_3Cl$: C 62.34, H 5.52, N 8.08; found C 61.94, H 5.54, N 8.05.

Example 7

N-1-[6-(2-Naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea

a) 6-(2-Naphthylmethoxy)-1-tetralone To a solution of 6-hydroxy-1-tetralone (see example 1, 1.65 g, 9.4 mmol) in DMF (20 mL) was added sodium hydride (0.30 g of 80% suspension in mineral oil, 9.4 mmol). After the evolution of hydrogen ceased, 2-(chloromethyl)naphthalene (1.77 g, 10.0 mmol) was added, and the resulting mixture was stirred at room temperature for 1 h. The solvent was concentrated under reduced pressure and the residue partitioned between EtOAc and 3N HCl. The organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue

was purified by flash chromatography eluting with CH_2Cl_2 to provide 1.92 g (68% yield) of the alkylated tetralone.
250 MHz ^{1}H NMR ($CDCl_3$) : δ 8.05 - 7.85 (m, 4H); 7.52 (m, 4H); 6.96 (dd, 1H); 6.86 (d, 1H); 5.53 (s, 2H); 2.93 (t, 2H); 2.61 (t, 2H); 2.10 (m, 2H).

b) 6-(2-Naphthylmethoxy)-1-tetralone oxime To a solution of 6-(2-naphthylmethoxy)-1-tetralone (1.80 g, 6.0 mmol) in dry pyridine (50 mL) was added hydroxylamine hydrochloride (0.83 g, 11.9 mmol). The resulting mixture was heated at 50°C for 15 min and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH to provide 1.67 g of the oxime (88% yield).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 8.05 (m, 1H); 7.92 (m, 3H); 7.65 - 7.45 (m, 4H); 6.92 (dd, 1H); 6.84 (d, 1H); 5.50 (s, 2H); 2.83 (t, 2H); 2.78 (t, 2H); 1.88 (m, 2H).

c) N-1-[6-(2-Naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine To a solution of 6-(2-naphthylmethoxy)-1-tetralone oxime (1.67 g, 5.3 mmol) in 1 : 2 EtOH/ THF (30 mL) was added BH_3·pyridine (1.6 mL, 15.8 mmol). The resulting mixture was stirred at room temperature overnight, at which time 3N HCl (18 mL) was added dropwise. The reaction mixture was stirred at room temperature for 4 h. Sodium carbonate was added and the mixture extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl. Removal of the solvent *in vacuo* provided the desired hydroxyamine (1.54 g, 92% yield).

d) N-1-[6-(2-Naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea
To a solution of N-1-[6-(2-naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine (1.50 g, 4.7 mmol) in THF (20 mL) was added trimethylsilyl isocyanate (1.27 mL, 9.4 mmol). The resulting mixture was heated at 60°C and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O to provide 584 mg (34% yield) of the hydroxyurea. m.p. 169 - 170°C.
250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d_4) : δ 8.08 (m, 1H); 7.90 (m, 2H); 7.53 (m, 4H); 7.23 (d, 1H); 6.90 (dd, 1H); 6.81 (br s, 1H); 5.48 (s, 2H); 5.45 (br t, 1H); 2.78 (m, 2H); 2.05 (m, 3H); 1.80 (m, 1H).
IR (cm^{-1}) : 3490, 3460, 3320 - 3160, 2900, 1650.
CIMS/ NH_3 (m/e, rel. int.) : 347 (26); 302 (25); 287 (76); 158 (26); 147 (100).

Example 8

N-1-[6-(2-Phenylethyl)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea

a) 6-(1-Tetralonyl) trifluoromethylsulfonate To a solution of 6-hydroxy-1-tetralone (see example 1, 324 mg, 2.0 mmol) in CH_2Cl_2 at -30°C was added trifluoromethanesulfonic anhydride (282 mg, 2.0 mmol), 2,6-lutidine (278 mg, 2.6 mmol) and dimethylaminopyridine (60 mg, 0.5 mmol). The resulting solution was allowed to warm to room temperature and stirred overnight. The solvent was removed *in vacuo*, and the residue was dissolved in EtOAc and filtered. The filtrate was washed successively with 10% HCl and H_2O. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography eluting with a gradient of EtOAc/ hexanes (0.5 - 2%) to provide the desired product (490 mg, 83%).
250 MHz ^{1}H NMR ($CDCl_3$) : d 8.12 (m, 1H); 7.20 (m, 2H); 3.00 (m, 2H); 2.68 (m, 2H); 2.15 (m, 2H).

b) 6-(2-Phenylethyl)-1-tetralone To a solution of 6-(1-tetralonyl) trifluoromethylsulfonate (447 mg, 1.5 mmol) in THF/ DMF (20 mL) was added a solution of triphenylethylborane (5.8 mL of 0.3 M solution, 1.7 mmol; prepared from styrene and borane-THF complex in THF), followed by K_2CO_3 (714 mg, 5.1 mmol) and HMPA (1 mL). The reaction mixture was deoxygenated, and tetrakis(triphenylphosphine)palladium (111 mg, 0.1 mmol) was added. The reaction mixture was again deoxygenated and heated at 50°C overnight. The reaction mixture was allowed to cool and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed successively with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with a gradient of EtOAc/ hexanes (0.8 - 3%) to provide the desired product (274 mg, 73%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.94 (d, 1H); 7.30 - 7.02 (m, 7H); 2.93 (s, 4H); 2.92 (t, 2H); 2.63 (t, 2H); 2.05 (m, 2H).

c) 6-(2-Phenylethyl)-1-tetralone oxime To a solution of 6-(2-phenylethyl)-1-tetralone (5.01 g, 20.1 mmol) in dry pyridine (40 mL) was added hydroxylamine hydrochloride (2.79 g, 40.2 mmol). The resulting mixture was heated at 50°C for 30 min and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from ethanol to provide 5.26 g of the oxime (99% yield).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.81 (d, 1H); 7.24 (m, 5H); 7.04 (dd, 1H); 6.99 (br s, 1H); 2.90 (s, 4H); 2.83 (t, 2H); 2.73 (t, 2H); 1.88 (m, 2H).

d) N-1-[6-(2-Phenylethyl)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine To a solution of 6-(2-phenylethyl)-1-tetralone oxime (4.63 g, 17.5 mmol) in 1 : 2 EtOH/ THF (35 mL) was added BH_3·pyridine (1.10 mL, 11.0 mmol) at 0°C, followed by the dropwise addition of 3N HCl (12 mL). The reaction mixture was stirred at room temperature overnight. Thin layer chromatographic analysis indicated an incomplete reaction, and additional BH_3·pyridine (1.1 mL, 11.0 mmol) was added, followed by 3N HCl (12 mL). The reaction mixture was stirred at room temperature for 1 h, and additional BH_3·pyridine was added (1.1 mL, 11 mmol), followed by 3 N HCl (15 mL). The mixture was stirred an additional 5 h at room temperature. The solvent was removed under reduced pressure; 3N HCl was added (40 mL), and the reaction mixture was stirred at room temperature for 1 h. Sodium carbonate was added and the mixture extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl. Removal of the solvent *in vacuo* provided the hydroxyamine (4.30 g, 92% yield).

e) N-1-[6-(2-Phenylethyl)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea
To a solution of N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine (3.1 g, 11.6 mmol) in THF (30 mL) was added trimethylsilyl isocyanate (3.1 mL, 23.2 mmol). The resulting mixture was heated at 50°C for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O and recrystallized from CH_2Cl_2 to provide 1.30 g (36% yield) of the hydroxyurea. m.p. 162 - 163°C.

250 MHz ^{1}H NMR ($CDCl_3$) : d 7.24 (m, 6H); 7.03 (dd, 1H); 6.95 (s, 1H); 5.49 (br t, 1H); 5.40 (s, 1H); 5.27 (br s, 2H); 2.89 (m, 4H); 2.74 (m, 2H); 2.05 (m, 3H); 1.79 (m, 1H).

IR (cm-1) : 3480, 3330 - 3100, 2920, 2860, 1660.

CIMS/ NH_3 (m/e, rel. int.) : 311 ($M+H^+$, 15); 250 (40); 235 (100).

Anal. Calc. for $C_{19}H_{22}N_2O_2$·3/8 H_2O : C 71.96, H 7.23, N 8.83; found C 71.87, H 7.01, N 8.97.

Example 9

N-1-[6-(2-Quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea

a) 6-(2-Quinolinylmethyloxy)-1-tetralone To a solution of 6-hydroxy-1-tetralone (see example 1; 3.21 g, 19.8 mmol) in DMF (50 mL) was added sodium hydride (0.75 g of 80% suspension in mineral oil, 25.0 mmol). After the evolution of hydrogen, 2-(chloromethyl)quinoline monohydrochloride (5.08 g, 23.7 mmol) which had previously been treated with saturated aqueous K_2CO_3 was added, and the resulting mixture was

heated at 50°C for 2 h. The reaction mixture was allowed to cool and was concentrated under reduced pressure. The residue was partitioned between EtOAc and 3 N HCl, and the organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with CH_2Cl_2 to provide the desired product (3.03 g, 51%).

b) 6-(2-Quinolinylmethyloxy)-1-tetralone oxime To a solution of 6-(2-quinolinylmethyloxy)-1-tetralone (3.00 g, 9.9 mmol) in dry pyridine was added hydroxylamine hydrochloride (1.37 g, 19.7 mmol). The resulting mixture was heated at 50°C for 30 min and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH to provide the oxime (950 mg, 30%). 250 MHz ^{1}H NMR ($CDCl_3$) : δ 8.30 (d, 1H); 8.08 (d, 1H); 7.92 - 7.56 (m, 5H); 6.89 (dd, 1H); 6.81 (d, 1H); 5.38 (s, 2H); 2.75 (m, 4H); 1.85 (m, 2H).

c) N-1-[6-(2-Quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine To a solution of 6-(2-quinolinylmethyloxy)-1-tetralone oxime (0.95 g, 3.0 mmol) in CH_2Cl_2 was added BH_3·pyridine (1.0 mL, 10.0 mmol), followed by glacial acetic acid (3 mL). The resulting mixture was heated at reflux for 5 h and allowed to cool. The solvent was removed under reduced pressure, 3 N HCl was added (10 mL) and the mixture was stirred at room temperature overnight. Sodium carbonate was added and the mixture extracted with CH_2Cl_2 (4x). The organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo* to provide the desired hydroxyamine (0.92 g, 96%), which was used without further purification.

d) N-1-[6-(2-Quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea To a solution of N-1-[6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine (0.90g, 2.8 mmol) in THF (20 mL) was added trimethylsilyl isocyanate (0.76 mL, 5.6 mmol). The resulting mixture was heated at 60°C for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O and purified by flash chromatography, eluting with CH_2Cl_2 to afford the desired hydroxyurea (0.31 g, 30%). m.p. 180.5 - 182.0°C.
250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d_4): δ 8.30 (d, 1H); 8.08 (d, 1H); 7.88 (d, 1H); 7.72 - 7.50 (m, 3H); 7.20 (d, 1H); 6.85 (dd, 1H); 6.77 (d, 1H); 5.40 (br t, 1H); 5.32 (s, 2H); 2.73 (m, 2H); 2.02 (m, 3H); 1.80 (m, 1H).
IR (cm^{-1}): 3480, 3330, 3200, 2960 - 2870, 1660.
CIMS (NH_3), m/e (rel. int.): 364 [$(M+H)^+$, 17]; 305 (75); 288 (85); 144 (100).

Anal. calc. for $C_{21}H_{21}N_3O_3 \cdot 1/2\ H_2O$: C 67.72, H 5.95, N 11.28; found C 67.92, H 5.84, N 11.04.

Example 10

N-3-(6-Benzyloxy-2,3-dihydro)benzofuranyl-N-hydroxyurea

a) 2-Chloro-1-(2,4-dihydroxyphenyl)-1-ethanimine, hydrochloride. To a solution of resorcinol (250 g, 2.27 mol) in Et_2O (1 L) was added chloroacetonitrile (208 g, 2.75 mol) and $ZnCl_2$ (172 g, 1.26 mol). To the resulting mixture was passed dry HCl gas over 40 min, maintaining the temperature at 25°C. The resulting cloudy mixture was then cooled to 15°C, with stirring, and a pinkish precipitate formed. The mixture was allowed to warm to room temperature and stirred for 18 h. The white solid which formed was collected by filtration and washed with Et_2O (2 L) and dried to provide the title compound (602 g, 100%).

b) 2-Chloro-1-(2,4-dihydroxyphenyl)-1-ethanone. 2-Chloro-1-(2,4-dihydroxyphenyl)-1-ethanimine, hydrochloride (504 g, 2.27 mol) was placed in H_2O (5 L), and heated at reflux for 1 h, then allowed to cool to room temperature. A seed crystal was added, and the mixture was stirred overnight. The solid which formed was collected by filtration, washed with H_2O (3 L) and dried to afford the title compound (280 g, 66%) as a pale orange solid.

c) 2,3-Dihydro-6-hydroxy-3-oxobenzofuran. To a solution of 2-chloro-1-(2,4-dihydroxyphenyl)-1-ethanone (11.0 g, 0.059 mol) in absolute EtOH (150 mL) was added sodium acetate (7.5 g, 0.092 mol), and the resulting mixture was heated at reflux for 1 h. The mixture was allowed to cool to 5°C, and the solid which formed was collected by filtration and washed with EtOH (25 mL). The solid was suspended in H_2O (100 mL), stirred for 20 min and filtered. The solid was dried at 40°C to afford the title compound (7.0 g, 79%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.50 (d, 1H); 6.57 (dd, 1H); 6.50 (d, 1H); 4.62 (s, 2H); 4.15 (br s, 1H).

d) 6-Benzyloxy-3-oxo-2,3-dihydrobenzofuran. To a solution of 2,3-dihydro-6-hydroxy-3-oxobenzofuran (363 g, 2.42 mol) in DMF (4 L) was added anhydrous potassium carbonate (668 g, 4.84 mol). After stirring for 5 min at room temperature, benzyl bromide (582 g, 3.40 mol) was added to the mixture dropwise over 15 min. The resulting mixture was stirred at room temperature for 18 h, at which time the potassium carbonate was removed by filtration and washed with DMF. The combined organic material was poured into cold H_2O

(12 L) and stirred. The solid which formed was collected by filtration, washed with H_2O (4 L) and dried to provide the title compound (554 g, 100%).

e) 6-Benzyloxy-3-oximino-2,3-dihydrobenzofuran. To a solution of 6-benzyloxy-3-oxo-2,3-dihydrobenzofuran (5.8 g, 25 mmol) in dry pyridine (38 mL) was added hydroxylamine hydrochloride (3.5 g, 50 mmol). The resulting mixture was heated at 50°C for 1 h, then allowed to cool to room temperature and poured into cold H_2O (100 mL). The resulting suspension was stirred for 15 min. The solid which formed was collected by filtration, washed with cold H_2O (30 mL) and dried to afford the oxime as a yellow solid (5.9 g, 92%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.45 (d, 1H); 7.40 (m, 5H); 6.64 (dd, 1H); 6.55 (d, 1H); 5.17 (s, 2H); 5.07 (s, 2H); 4.07 (br s, 1H).

f) N-3-(6-Benzyloxy-2,3-dihydro)benzofuranyl-N-hydroxyamine. To a solution of 6-benzyloxy-3-oximino-2,3-dihydrobenzofuran (505 g, 1.98 mol) in 1 : 1 MeOH/ CH_2Cl_2 (10 L) was added BH_3·pyridine (808 g, 8.69 mol). To the resulting mixture was added dropwise over 1.25 h, 6 N HCl (1.5 L), and the solution which resulted was allowed to stir for 18 h at room temperature. Activated carbon (100 g) was added, and the mixture was stirred for 1 h, filtered and concentrated under reduced pressure. The concentrate was cooled to 10°C, and 3 N HCl (2 L) was added cautiously. The resulting suspension was stirred for 1 h at room temperature, then cooled to 5°C. The solid which formed was collected by filtration and suspended in cold H_2O. The pH was adjusted to pH 10.5, and the mixture was stirred for 1 h. The mixture was filtered and the solid was washed with H_2O and dried to afford the title compound (440 g, 86%).

g) N-3-(6-Benzyloxy-2,3-dihydro)benzofuranyl-N-hydroxyurea. To a solution of N-3-(6-benzyloxy-2,3-dihydro)benzofuranyl-N-hydroxyamine (100 g, 0.39 mol) in THF (2.3 L) was added decolorizing activated carbon (Norit A, 10 g), and the resulting mixture was stirred for 15 min. The mixture was filtered, and to the filtrate was added in one portion under an argon atmosphere trimethylsilylisocyanate (77 mL, 0.57 mol). The resulting mixture was heated at 55°C for 1 h, at which time HPLC analysis indicated that the reaction was incomplete. Additional trimethylsilylisocyanate was added (23 mL, 0.17 mol), and heating at 55°C was continued for an additional 30 min. The reaction mixture was allowed to cool to room temperature. After stirring overnight, the mixture was cooled to 5°C. The solid which formed was collected by filtration, washed with THF (250 mL) and dried at 40°C to afford the title compound as a white powder (62 g, 53%). m.p. 174.5 - 175.5°C
250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d4): d 7.45 - 7.25 (m, 5H); 7.14 (d, 1H); 6.51 (dd, 1H); 6.41 (d, 1H); 5.87 (t, 1H); 5.03 (s, 2H); 4.53 (d, 1H).

IR (cm^{-1}): 3460, 3320, 3180, 2880, 1650 - 1620.
Anal. calc. for $C_{16}H_{16}N_2O_4 \cdot 3/8\ H_2O$: C 62.58, H 5.50, N 9.12; found C 62.62, H 5.34, N 9.24.

Example 11

N-2-(7-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

a) 7-Methoxy-2-tetralone oxime To a solution of 7-methoxy-2-tetralone (499 mg, 2.83 mmol) in dry pyridine (2 mL) was added hydroxylamine hydrochloride (399 mg, 5.80 mmol). The resulting mixture was heated at 50°C for 1 h. The solvent was concentrated under reduced pressure, and the solid residue was recrystallized from ethanol to provide the oxime (511 mg, 95%) which was used without further purification.

b) N-2-(7-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine To a solution of 7-methoxy-2-tetralone oxime (500 mg, 2.6 mmol) in 1 : 2 EtOH/ THF (15 mL) at 0°C was slowly added $BH_3 \cdot$pyridine (0.52 mL, 5.2 mmol), followed by 3 N HCl (1.5 mL). The resulting mixture was allowed to warm to room temperature and stirred for 2 h. Sodium carbonate was added, and the mixture was extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl, and dried ($MgSO_4$). Removal of the solvent *in vacuo* provided the desired hydroxyamine (171 mg, 34%) which was used without further purification.

c) N-2-(7-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea To a solution of N-2-(7-methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine (150 mg, 0.78 mmol) in dry THF (5 mL) was added trimethylsilyl isocyanate (0.78 mL, 1.56 mmol), and the resulting mixture was heated at 50°C for 1 h. The solvent was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O and recrystallized from CH_2Cl_2 and MeOH to provide the hydroxyurea (88 mg, 48% yield).
m.p. 152 - 53°C.
250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d4) : δ 7.00 (d, 1H); 6.69 (dd, 1H); 6.64 (d, 1H); 4.42 (m, 1H); 3.10 (dd, 1H); 2.85 (m, 3H); 1.96 (dd, 2H).
IR (cm^{-1}) : 3500, 3330, 3160, 2900, 1640.
CIMS/ NH_3 (m/e, rel. int.) : 237 ($M+H^+$, 49); 221 (15); 194 (65); 178 (100).

Example 12

N-1-(7-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

a) 7-Hydroxy-1-tetralone To a solution of ethanethiol (8.4 mL, 0.114 mol) in dry DMF (75 mL) was added slowly sodium hydride (1.6 g of 80% suspension in mineral oil, 57 mmol). After the evolution of hydrogen ceased, 7-methoxy-1-tetralone (5.14 g, 29 mmol) was added, and the resulting mixture was heated at 150°C for 3 h. The mixture was allowed to cool and was concentrated under reduced pressure. The residue was partitioned between EtOAc and 3 N HCl, and the organic extract was washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). Removal of the solvent *in vacuo* and trituration of the residue with CH_2Cl_2 provided the hydroxy tetralone (3.27 g, 69%) which was used without further purification.
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.40 (d, 1H); 7.15 (d, 1H); 7.00 (dd, 1H); 2.90 (t, 2H); 2.63 (t, 2H); 2.12 (m, 2H).

b) 7-Benzyloxy-1-tetralone To a solution of 7-hydroxy-1-tetralone (2.01 g, 12.4 mmol) in dry DMF (50 mL) was added slowly sodium hydride (0.60 g of 80% suspension in mineral oil, 18.6 mmol). After the evolution of hydrogen ceased, benzyl chloride (2.47 g, 18.6 mmol) was added, and the resulting mixture was heated at 60°C for 30 min. The mixture was allowed to cool and was partitioned between EtOAc and 3 N HCl. The organic extract was washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 2 : 3 CH_2Cl_2/ hexanes to provide the desired tetralone as a white crystalline solid (1.69 g, 54%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.62 (d, 1H); 7.46 - 7.10 (m, 7H); 5.10 (s, 2H); 2.90 (t, 2H); 2.64 (t, 2H); 2.10 (m, 2H).

c) 7-Benzyloxy-1-tetralone oxime To a solution of 7-benzyloxy-1-tetralone (1.53 g, 6.1 mmol) in dry pyridine (20 mL) was added hydroxylamine hydrochloride (0.81 g, 12.1 mmol). The resulting mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH/ H_2O to provide the desired oxime (1.52 g, 99%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.53 (d, 1H); 7.49 - 7.24 (m, 5H); 7.05 (d, 1H); 6.92 (dd, 1H); 5.06 (s, 2H); 2.80 (t, 2H); 2.70 (t, 2H); 1.85 (m, 2H).

d) N-1-(7-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine To a solution of 7-benzyloxy-1-tetralone oxime (107 mg, 0.42 mmol) in ethanol (5 mL) was added BH_3·pyridine (0.14 mL, 1.4 mmol). The solution was cooled to 0°C, and 3 N HCl (1.4 mL) was added dropwise. The resulting mixture was allowed to warm to room temperature

and stirred for 2 h. Sodium carbonate was added, and the mixture was extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo* to provide the desired hydroxyamine (100 mg, 95%), which was used without further purification.

e) N-1-(7-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea To a solution of N-1-(7-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine (1.10 g, 4.3 mmol) in dry THF (20 mL) was added trimethylsilyl isocyanate (1.2 mL, 8.7 mmol). The resulting mixture was heated at 60°C for 30 min, then allowed to cool to room temperature and stirred overnight. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O to provide the desired hydroxyurea (858 mg, 64%). m.p. 158 - 161°C.

250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d_4): δ 7.47 - 7.30 (m, 5H); 7.00 (d, 1H); 6.95 (d, 1H); 6.82 (dd, 1H); 5.43 (br t, 1H); 5.02 (s, 2H); 2.72 (m, 2H); 2.00 (m, 3H); 1.78 (m, 1H).

IR (cm^{-1}): 3470, 3330 - 3100, 2930, 2870, 1670 - 1630.

CIMS (CH_4), m/e (rel. int.): 313 (M^+, 3); 252 (34); 237 (100); 236 (38); 91 (86).

Anal. calc. for $C_{18}H_{20}N_2O_3$: C 69.21, H 6.45, N 8.97; found C 69.15, H 6.52, N 8.95.

Example 13

N-1-(6-Phenyl-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

a) 6-Phenyl-1-tetralone To a solution of zinc chloride (5.1 mL of 1.0 M solution, 5.1 mmol) in dry THF (20 mL) was added phenyl lithium (2.6 mL of 2.0 M solution, 5.1 mmol). The resulting mixture was stirred at room temperature for 30 min and added to a solution containing 6-(1-tetralonyl) trifluoromethylsulfonate (1.09 g, 3.7 mmol, see example 8 for preparation), palladium acetate (7.6 mg, 0.03 mmol) and bis(1,3-diphenylphosphino)-propane (14 mg, 0.03 mmol) in dry THF (50 mL). The resulting mixture was stirred at room temperature for 1 h, and then partitioned between EtOAc and 3 N HCl. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 10% EtOAc/ hexanes to provide the desired product which was recrystallized from hexanes (0.42 g, 51%).

250 MHz ^{1}H NMR ($CDCl_3$) : δ 8.10 (d, 1H); 7.66 - 7.35 (m, 7H); 3.03 (t, 2H); 2.70 (t, 2H); 2.20 (m, 2H).

b) 6-Phenyl-1-tetralone oxime To a solution of 6-phenyl-1-tetralone (99 mg, 0.4 mmol) in dry pyridine (6 mL) was added hydroxylamine hydrochloride (90 mg, 1.3 mmol). The resulting mixture was stirred at room temperature for 30 min. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH to provide the desired oxime (85 mg, 81%).
250 MHz ^{1}H NMR ($CDCl_3$/ MeOH-d_4) : δ 7.96 (d, 1H); 7.63 - 7.33 (m, 7H); 2.85 (2t, 4H); 1.92 (m, 2H).

c) N-1-(6-Phenyl-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine To a solution of 6-phenyl-1-tetralone oxime (352 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added BH_3·pyridine (0.6 mL, 6.0 mmol), followed by glacial acetic acid (1.5 mL). The resulting mixture was heated at reflux for 2 h and allowed to cool. The solvent was removed under reduced pressure, 3 N HCl was added (5 mL) and the mixture was stirred at room temperature for 2 h. Sodium carbonate was added and the mixture extracted with CH_2Cl_2 (4x). The organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo* to provide the desired hydroxyamine (270 mg, 75%), which was used without further purification.
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.60 - 7.30 (m, 8H); 4.17 (t, 1H); 2.85 (m, 2H); 2.25 (m, 1H); 2.05 - 1.73 (m, 3H).

d) N-1-(6-Phenyl-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea To a solution of N-1-(6-phenyl-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine (270 mg, 1.1 mmol) in dry THF (10 mL) was added trimethylsilyl isocyanate (0.30 mL, 2.2 mmol). The resulting mixture was heated at 60°C for 1 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was triturated with Et_2O and recrystallized from CH_2Cl_2/ hexanes. Further purification by flash chromatography, eluting with a solvent gradient of MeOH/ CH_2Cl_2 provided the desired hydroxyurea (70 mg, 23%). m.p. 175 - 176°C.
250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d_4): d 7.57 (d, 2H); 7.46 - 7.32 (m, 6H); 5.53 (br t, 1H); 2.85 (m, 2H); 2.07 (m, 3H); 1.84 (m, 1H).
IR (cm^{-1}): 3490, 3320 - 3160, 2930, 2860, 1640, 1630.
CIMS (NH_3), m/e (rel. int.): 283 [$(M+H)^+$, 12]; 267 (22); 222 (37); 207(100).
Anal. calc. for $C_{17}H_{18}N_2O_2\cdot 1/4\ H_2O$: C 71.18, H 6.50, N 9.77; found C 71.06, H 6.42, N 9.74.

Example 14

N-1-[5-(4-Methoxybenzyloxy)indanyl]-N-hydroxyurea

a) 5-(4-Methoxybenzyloxy)-1-indanone To a solution of 5-hydroxy-1-indanone (1.30 g, 8.8 mmol, see example 2 for preparation) in dry DMF (25 mL) was added slowly sodium hydride (0.26 g of 80% suspension in mineral oil, 8.8 mmol). After the evolution of hydrogen ceased, 4-methoxybenzyl chloride (1.50 g, 10.6 mmol) was added, and the resulting mixture was stirred at 60°C for 1 h. The mixture was allowed to cool and was partitioned between EtOAc and 3 N HCl. The organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with CH_2Cl_2 to provide the desired product (1.76 g, 75%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.70 (d, 1H); 7.35 (d, 2H); 6.96 (m, 4H); 5.05 (s, 2H); 3.82 (s, 3H); 3.10 (dd, 2H); 2.69 (dd, 2H).

b) 5-(4-Methoxybenzyloxy)-1-indanone oxime To a solution of 5-(4-methoxybenzyloxy)-1-indanone (1.74 g, 6.5 mmol) in dry pyridine (40 mL) was added hydroxylamine hydrochloride (0.90 g, 13.0 mmol). The resulting mixture was heated at 60°C for 1 h. The solvent was removed *in vacuo*, and the residue was recrystallized from EtOH/ H_2O to provide the desired oxime (1.32 g, 72%).

c) N-1-[5-(4-Methoxybenzyloxy)indanyl]-N-hydroxy-amine To a solution of 5-(4-methoxybenzyloxy)-1-indanone oxime (1.30 g, 4.6 mmol) in CH_2Cl_2 (25 mL) was added BH_3·pyridine (1.84 mL, 18.4 mmol), followed by glacial acetic acid (4.6 mL). The resulting mixture was heated at reflux for 4 1/2 h and allowed to cool. The solvent was removed under reduced pressure, 3 N HCl was added (15 mL), and the mixture was stirred at room temperature overnight. Saturated aqueous sodium carbonate was added with cooling, and the mixture extracted with CH_2Cl_2 (2x) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by flash chromatography, eluting with a gradient of MeOH/ CH_2Cl_2 to provide the desired hydroxyamine (227 mg, 17%).
250 MHz ^{1}H NMR ($CDCl_3$) : δ 7.31 (m, 3H); 6.86 (m, 4H); 5.42 (br, 1H); 4.98 (s, 2H); 4.50 (dd, 1H); 3.82 (s, 3H); 3.02 (m, 1H); 2.81 (m, 1H); 2.30 (m, 1H); 2.10 (m, 1H); 1.60 (br, 1H).

d) N-1-[5-(4-Methoxybenzyloxy)indanyl]-N-hydroxyurea To a solution of N-1-[5-(4-methoxybenzyloxy)indanyl]-N-hydroxyamine (220 mg, 0.8 mmol) in dry THF (4 mL) was added trimethylsilyl isocyanate (0.21 mL, 1.5 mmol). The resulting mixture was heated at 60°C for 1 h, then allowed to cool to room temperature and stirred overnight. The solvent

was removed under reduced pressure and the residue was triturated with Et_2O. Purification by flash chromatography eluting with a gradient of MeOH/ CH_2Cl_2 provided the desired hydroxyurea (154 mg, 61%). m.p. 166 - 167°C.

250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d4): d 7.35 (d, 2H); 7.18 (d, 1H); 6.92 (d, 2H); 6.82 (m, 2H); 5.78 (dd, 1H); 4.97 (s, 2H); 3.04 (m, 1H); 2.82 (m, 1H); 2.45 - 2.14 (m, 2H).

IR (cm^{-1}): 3400, 3350, 3290, 3100, 2870, 1690, 1615.

CIMS (NH_3), m/e (rel. int.): 346 (23); 330 (25); 284 (22); 268 (34); 253 (100); 133 (36); 121 (39).

Anal. calc. for $C_{18}H_{20}N_2O_4$: C 65.84, H 6.14, N 8.53; found C 65.54, H 6.15, N 8.52.

Example 15

N-3-[6-(4-Methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea

a) 2,3-dihydro-6-hydroxy-3-oxobenzofuran (see Example 10, 1.93 g, 12.9 mmol) in DMF (35 mL) was added sodium hydride (0.46 g of 80% suspension in mineral oil, 15.5 mmol). After the evolution of hydrogen, 4-methoxybenzyl chloride (2.19 g, 15.5 mmol) was added, and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was partitioned between EtOAc and 3 N HCl, and the organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 2% MeOH/ CH_2Cl_2 to provide 2.46 g (69% yield) of the desired product.

b) 6-(4-Methoxybenzyloxy)-3-oximino-2,3-dihydrobenzofuran. To a solution of 6-(4-methoxybenzyloxy)-3-oxo-2,3-dihydrobenzofuran (2.46 g, 9.1 mmol) in dry pyridine (10 mL) was added hydroxylamine hydrochloride (1.24 g, 18.0 mmol). The resulting mixture was heated at 50°C for 2 h and allowed to cool to room temperature. The solvent was removed *in vacuo*, and the residue was recrystallized first from EtOH/ H_2O and a second time from CH_2Cl_2 to provide 739 mg of the oxime (29% yield).

c) N-3-[6-(4-Methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine. To a solution of 6-(4-methoxybenzyloxy)-3-oximino-2,3-dihydrobenzofuran (739 mg, 2.6 mmol) in CH_2Cl_2 (8 mL) was added BH_3·pyridine (1.00 mL, 10.0 mmol) followed by glacial acetic acid (2.6 mL). The resulting mixture was heated at reflux for 5 h, allowed to cool to room temperature and concentrated under reduced pressure. The residue was treated with 3 N HCl (10 mL), and the mixture was stirred at room temperature for 2 h. Sodium carbonate was added, and the mixture was extracted with CH_2Cl_2. The organic extract was washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the

residue was purified by flash chromatography, eluting with 2% MeOH/ CH_2Cl_2 to provide the hydroxyamine (510 mg, 68%).

d) N-3-[6-(4-Methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea. To a solution of N-3-[6-(4-methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine (510 mg, 1.78 mmol) in dry THF (10 mL) was added trimethylsilyl isocyanate (0.48 mL, 3.55 mmol). The resulting solution was heated at 60°C for 1 h and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was triturated with Et_2O and recrystallized from MeOH/ CH_2Cl_2 to provide the hydroxyurea (92 mg, 16%).
250 MHz ^{1}H NMR ($CDCl_3$, MeOH-d_4) : δ 7.35 (d, 2H); 7.20 (d, 1H); 6.91 (d, 2H); 6.56 (dd, 1H); 6.48 (d, 1H); 5.92 (t, 1H); 4.95 (s, 2H); 4.60 (d, 2H); 3.72 (s, 3H).
IR (cm^{-1}) : 3460, 3320, 3200 - 3120, 2950 - 2840, 1700 - 1610, 1600, 1580.
FAB MS, m/e (rel. int.) : 331[$(M+H)^+$, 58]; 330 (M^+, 73); 329 [$(M-H)^+$, 95]; 313 (48); 255 (55); 137 (100), 121 (100).
Anal. Calc. for $C_{17}H_{18}N_2O_5 \cdot 1/4\ H_2O$: C 60.98, H 5.57, N 8.37; found C 60.88, H 5.41, N 8.31.

Example 16

N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

a) 5-Benzyloxy-1-tetralone. To a mixture of potassium hydride (120 mg, 3.0 mmol) in DMF was added 5-hydroxy-1-tetralone (486 mg, 3.0 mmol), and the resulting mixture was stirred at room temperature for 1 h. To this mixture was then added benzyl bromide (0.38 mL, 3.2 mmol). After stirring at room temperature for an additional 1.5 h, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed successively with acidic H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo*, and the material was used without further purification.

b) 5-Benzyloxy-1-tetralone, oxime. To a solution of 5-benzyloxy-1-tetralone, prepared above, in 1 : 1 EtOH/ pyridine (25 mL) was added hydroxylamine hydrochloride (630 mg, 9.1 mmol), and the resulting mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with a solvent gradient of 0 - 20% EtOAc/ hexanes to afford the title compound (444 mg, 55% for two steps).

c) N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine. To a solution of 5-benzyloxy-1-tetralone, oxime (420 mg, 1.57 mmol) in EtOH was added $BH_3 \cdot$pyridine

(1.20 mL, 11.9 mmol). To this was added 3 N HCl until a slight effervescence was noted, and the reaction mixture was stirred at room temperature for several h. To the mixture was added excess 3 N HCl until the effervescence ceased, and the pH was then adjusted to pH 9 - 10 with 3 N NaOH. Water (200 mL) was added, and the solid which formed was collected by filtration and used without further purification. m.p. 108 - 110°C

[1]H NMR ($CDCl_3$) : δ 7.49 - 7.28 (m, 5H); 7.15 (t, 1H); 6.99 (d, 1H); 6.81 (d, 1H); 5.07 (s, 2H); 4.12 (apparent t, 1H); 2.99 - 2.84 (ddd, 1H); 2.67 - 2.51 (ddd, 1H); 2.22 (m, 1H); 1.99- 1.70 (m, 3H).

CIMS (NH_3); m/e (rel. int.) : 270 [$(M+H)^+$, 85], 254 (100), 237 (72).

Anal. Calc. for $C_{17}H_{19}NO_2$: C 75.81, H 7.11, N 5.20 ; found : C 75.83, H 7.31, N 5.24.

d) N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea. To a solution of N-1-(5-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine (350 mg, 1.49 mmol) in THF was added trimethylsilyl isocyanate (0.46 mL, 3.4 mmol). The resulting mixture was heated at reflux for 1 h and then allowed to cool. The solid which formed was collected by filtration and washed with Et_2O to afford the title compound (130 mg). The combined mother liquor and Et_2O washes were washed successively with dilute HCl, H_2O and saturated aqueous NaCl and dried. The solvent was removed under reduced pressure to afford additional hydroxyurea (200 mg total, 43%) as a white crystaline solid. m.p. 187 - 188°C

[1]H NMR ($CDCl_3$, MeOH-d4) : δ 7.39 - 7.20 (m, 5H); 7.04 (t, 1H); 6.82 (d, 1H); 6.70 (d, 1H); 5.40 (br t, 1H); 4.96 (s, 2H); 3.40 - 3.29 (m, 2H); 2.03 - 1.85 (m, 3H); 1.69 (m, 1H).

CIMS (NH_3); m/e (rel. int.) : 330 [$(M+NH_4)^+$, 79], 313 [$(M+H)^+$, 71], 297 (39), 270 (55); 254 (100), 237 (85).

Anal. Calc. for $C_{18}H_{20}N_2O_3$: C 69.21, H 6.45, N 8.97 ; found : C 68.93, H 6.55, N 8.99.

Example 17

N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

a) 5-Phenoxy-1-tetralone. To a solution containing 5-hydroxy-1-tetralone (970 mg, 6.0 mmol) and iodobenzene (4.0 mL, 35.7 mmol) in DMF (12 mL) was added slowly with cooling sodium hydride (150 mg, 6.25 mmol). The resulting mixture was heated until dissolution occurred, then allowed to cool. To the mixture was added slowly with cooling cuprous chloride (600 mg, 6.1 mmol), followed by tris[2-(2-methoxyethoxy)ethyl]amine (0.68 mL, 2.1 mmol). The resulting mixture was heated at 145 - 150°C overnight and then allowed to cool. The reaction mixture was partitioned between 3 N HCl and EtOAc and

filtered. The organic extract was washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with a solvent gradient of 0 - 5% EtOAc/ hexanes to afford the title compound (300 mg, 21%).
^{1}H NMR ($CDCl_3$) : δ 7.89 (dd, 1H); 7.40 - 7.25 (m, 3H); 7.10 (m, 2H); 6.94 (m, 2H); 2.93 (apparent t, 2H); 2.67 (dd, 2H); 2.14 (apparent quintet, 2H).

b) 5-Phenoxy-1-tetralone, oxime. To a solution of 5-phenoxy-1-tetralone (400 mg, 1.68 mmol) in 1 : 1 EtOH/ pyridine was added hydroxylamine hydrochloride (352 mg, 5.1 mmol), and the resulting mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was suspended in H_2O and the solid which formed was collected by filtration to afford the oxime (330 mg, 78%) which was used without further purification.

c) N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine. To a solution of 5-phenoxy-1-tetralone, oxime (330 mg, 1.3 mmol) in EtOH was added BH_3·pyridine (0.52 mL, 1.3 mmol). To this was added 3 N HCl until a slight effervescence was noted, and the reaction mixture was stirred at room temperature for several h. To the mixture was added excess 3 N HCl until the effervescence ceased, and the pH was then adjusted to pH 9 - 10 with 3 N NaOH. Water was added, and the solid which formed was collected by filtration and used without further purification (316 mg, 95%).
^{1}H NMR ($CDCl_3$) : δ 7.29 (m, 2H); 7.18 - 7.01 (m, 3H); 6.91 (m, 2H); 6.82 (dd, 1H); 4.17 (m, 1H); 2.90 - 2.78 (m, 1H); 2.62 - 2.49 (m, 1H); 2.27 - 2.15 (m, 1H); 1.95 - 1.71 (m, 3H).
CIMS (NH_3); m/e (rel. int.) : 256 [$(M+H)^+$, 100], 240 (88); 238 (74), 223 (39).
Anal. Calc. for $C_{16}H_{17}NO_2$: C 75.27, H 6.71, N 5.49 ; found : C 75.11, H 6.80, N 5.41.

d) N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea. To a solution of N-1-(5-phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine (255 mg, 1.0 mmol) in THF was added trimethylsilyl isocyanate (0.32 mL, 1.0 mmol). The resulting mixture was heated at reflux for 1 h and then allowed to cool. The reaction mixture was concentrated under reduced pressure, and Et_2O was added to the residue. The solid which formed was collected by filtration to afford the title compound (150 mg, 50%). m.p. 123 - 125^{o}C
^{1}H NMR ($CDCl_3$, MeOH-d_4) : δ 7.30 - 7.22 (m, 2H); 7.12 - 6.99 (m, 3H); 6.88 (m, 2H); 6.73 (m, 1H); 5.46 (m, 1H); 2.82 - 1.70 (m, 6H).
CIMS (NH_3); m/e (rel. int.) : 316 [$(M+NH_4)^+$, 46], 299 [$(M+H)^+$, 100].

Anal. Calc. for $C_{17}H_{18}N_2O_3$: C 68.44, H 6.08, N 9.39 ; found : C 68.18, H 6.04, N 9.54.

Example 18

N-1-(5-Phenoxyindanyl)-N-hydroxyurea

a) 3-Phenoxybenzyl bromide. To a solution containing 3-phenoxybenzyl alcohol (5.0 g, 25.0 mmol) and triphenylphosphine (7.2 g, 27.5 mmol) in CH_2Cl_2 (200 mL) under an argon atmosphere at -30°C was added, portionwise, N-bromosuccinimide (4.4 g, 25.0 mmol). The resulting mixture was stirred at -30°C for 1 h, and then concentrated under reduced pressure. The residue was filtered through silica gel, eluting with hexanes to afford the title compound as a colorless oil (4.73 g, 72%).

b) Diethyl 3-phenoxybenzylmalonate. To a suspension of sodium hydride (1.36 g of 60% dispersion in mineral oil, 33.9 mmol) in DMF (30 mL) under an argon atmosphere at 0°C was added, over 10 min, a solution of diethyl malonate (5.42 mL, 35.7 mmol) in DMF (20 mL). The reaction mixture was stirred at 0°C for 30 min, at which time a solution of 3-phenoxybenzyl bromide (4.7 g, 17.9 mmol) in DMF (25 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was partitioned between Et_2O and aqueous NH_4Cl, and the organic extract was washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 10% EtOAc/ hexanes to afford the title compound as a colorless oil (4.17 g, 68%).

c) 3-(3-Phenoxyphenyl)propanoic acid. To a solution of diethyl 3-phenoxybenzylmalonate (4.17 g, 12.2 mmol) in EtOH (100 mL) was added 1 M NaOH (61 mL, 60.9 mmol), and the resulting mixture was heated at reflux overnight. The mixture was allowed to cool, and the pH was adjusted to pH 4 by the addition of 1 M HCl. The mixture was diluted with CH_2Cl_2, and the organic layer was washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was dissolved in acetic acid and heated at reflux overnight. The reaction mixture was allowed to cool and was partitioned between CH_2Cl_2 and H_2O. The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic extracts were washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the title compound as a pale yellow oil (2.67 g, 90%).

d) 5-Phenoxy-1-indanone and 7-phenoxy-1-indanone. To a round-bottomed flask fitted with a mechanical stirrer was added polyphosphoric acid (600 g). To this was added over 1

h, 3-(3-phenoxyphenyl)propanoic acid (49 g, 0.202 mol), maintaining the temperature at 75°C. Upon completion of the addition, the resulting mixture was stirred for 1 h at 80°C, then cooled to 0°C and diluted with ice cold H_2O. Ether was added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous phase was extracted with Et_2O (2 x 200 mL). The combined organic extracts were washed successively with H_2O, saturated K_2CO_3, H_2O and saturated aqueous NaCl and dried (K_2CO_3). The solvent was removed *in vacuo*, and the residue was purified in portions by flash chromatography, eluting with 10% EtOAc/ hexanes. The major component which was isolated was recrystallized from cyclohexane to afford 5-phenoxy-1-indanone (4.63 g, 10%). m.p. 67 - 69°C

<u>^{1}H NMR</u> ($CDCl_3$) : δ 7.72 (d, 1H); 7.42 (t, 2H); 7.22 (m, 1H); 7.10 (d, 1H); 6.98 (d, 1H); 6.93 (s, 1H); 3.06 (dd, 2H); 2.71 (dd, 2H).

A minor component was also isolated and recrystallized from cyclohexane to afford 7-phenoxy-1-indanone (548 mg, 1%). m.p. 102 - 103°C

<u>e) 5-Phenoxy-1-indanone, oxime</u>. To a solution of 5-phenoxy-1-indanone (4.5 g, 19.9 mmol) in pyridine (30 mL) was added hydroxylamine hydrochloride (2.78 g, 39.9 mmol). The resulting mixture was heated at 50°C for 30 min and then allowed to cool. The mixture was concentrated under reduced pressure, and the residue was treated with H_2O (100 mL) and stirred for 1 h. The solid which formed was collected by filtration, washed with H_2O and dried under reduced pressure to afford the oxime (4.48 g, 94%) as a solid. m.p. 107 - 108°C

<u>f) N-1-(5-Phenoxyindanyl)-N-hydroxyamine</u>. To a solution of 5-phenoxy-1-indanone, oxime (6.38 g, 26.6 mmol) in 2 : 1 Et_2O/ MeOH (120 mL) under an argon atmosphere at 0°C was added BH_3·pyridine (11.78 mL, 116.6 mmol). The resulting mixture was allowed to warm to room temperature, and 2 N HCl (42 mL, 84.3 mmol) was added dropwise over 30 min. Upon completion of the addition, thin layer chromatographic analysis indicated that the reaction was incomplete, so additional BH_3·pyridine (3 mL, 30 mmol) was added. Stirring was continued for 30 min more, at which time 2 N HCl (25 mL, 50 mmol) was added dropwise. The pH was adjusted to pH 12 by the addition of 3 N NaOH. The mixture was extracted with CH_2Cl_2 (4 x 250 mL), and the combined organic extracts were washed successively with H_2O and saturated aqueous and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 25% EtOAc/ hexanes to afford the title compound as a white solid (5.1 g, 79%). m.p. 99 - 100°C

g) N-1-(5-Phenoxyindanyl)-N-hydroxyurea. To a solution of N-1-(5-phenoxyindanyl)-N-hydroxyamine (4.9 g, 20.3 mmol) in THF (100 mL) under an argon atmosphere was added trimethylsilyl isocyanate (2.75 mL, 40.6 mmol). The resulting mixture was heated to 60°C for 1.5 h, and then allowed to cool. The mixture was concentrated under reduced pressure, and the solid residue was recrystallized from EtOH to afford the title compound as a white solid (3.05 g, 53%). m.p. 172 - 173°C
CIMS (NH_3); m/e (rel. int.) : 302 [$(M+NH_4)^+$, 9], 285 [$(M+H)^+$,10], 209 (100).
Anal. Calc. for $C_{16}H_{16}N_2O_3$: C 67.59, H 5.67, N 9.85; found : C 67.51, H 5.72, N 9.90.

Example 19
N-1-[5-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea

a) 5-(4-Fluorophenoxy)-1-tetralone. To a solution containing 5-hydroxy-1-tetralone (1.0 g, 6.1 mmol) and p-difluorobenzene (4.4 mL, 42.4 mmol) in DMF (13 mL) was added slowly with cooling sodium hydride (160 mg, 6.67 mmol). The resulting mixture was heated until dissolution occurred, then allowed to cool. To the mixture was added slowly with cooling cuprous chloride (585 mg, 6.1 mmol), followed by tris[2-(2-methoxyethoxy)ethyl]amine (0.68 mL, 2.1 mmol). The resulting mixture was heated at 145 - 150°C overnight and then allowed to cool. The reaction mixture was partitioned between 3 N HCl and EtOAc and filtered. The organic extract was washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford the title compound (250 mg, 16%).
^{1}H NMR ($CDCl_3$) : δ 7.83 (d, 1H); 7.26 (t, 1H); 7.03 (m, 3H); 6.91 (m, 2H); 2.94 (t, 2H); 2.66 (dd, 2H); 2.12 (apparent quintet, 2H).
CIMS (NH_3), m/e (rel. int.) : 274 [$(M+NH_4)^+$, 100], 257 [$(M+H)^+$, 42].

b) 5-(4-Fluorophenoxy)-1-tetralone, oxime. To a solution of 5-(4-fluorophenoxy)-1-tetralone (250 mg, 1.0 mmol) in 1 : 1 EtOH/ pyridine (4 mL) was added hydroxylamine hydrochloride (210 mg, 3.0 mmol), and the resulting mixture was allowed to stir overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was suspended in H_2O and the solid which formed was collected by filtration to afford the oxime (160 mg, 62%) which was used without further purification.

c) N-1-[5-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine. To a solution of 5-(4-fluorophenoxy)-1-tetralone, oxime (150 mg, 0.55 mmol) in EtOH was added BH_3·pyridine (0.40 mL, 4.0 mmol). To this was added 3 N HCl until a slight effervescence was noted, and the reaction mixture was stirred at room temperature for

several h. To the mixture was added excess 3 N HCl until the effervescence ceased, and the pH was then adjusted to pH 9 - 10 with 3 N NaOH. Water was added, and the solid which formed was collected by filtration and used without further purification (79 mg, 53%).

d) N-1-[5-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea. To a solution of N-1-[5-(4-fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine (79 mg, 0.29 mmol) in THF was added trimethylsilyl isocyanate (0.10 mL, 0.74 mmol). The resulting mixture was heated at reflux for 1 h and then allowed to cool. The reaction mixture was concentrated under reduced pressure, and Et_2O was added to the residue. The solid which formed was collected by filtration to afford the title compound (40 mg, 44%).
^{1}H NMR ($CDCl_3$, MeOH-d4) : δ 7.08 (m, 2H); 6.97 (m, 2H); 6.84 (m, 2H); 6.68 (dd, 1H); 5.49 (m, 1H); 2.84 - 2.50 (m, 2H); 2.00 (m, 3H); 1.74 (br m, 1H).
CIMS (NH_3), m/e (rel. int.) : 334 [$(M+NH_4)^+$, 41], 317 [$(M+H)^+$, 100].
Anal. Calc. for $C_{17}H_{17}FN_2O_3$: C 64.55, H 5.42, N 8.86; found : C 62.15, H 5.51, N 9.17.

Example 20
N-1-[6-(2-Pyridinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea

a) 6-(2-Pyridinylmethoxy)-1-tetralone. To a solution containing 6-hydroxy-1-tetralone (500 mg, 3.08 mmol) and 2-picolyl chloride, hydrochloride (556 mg, 3.39 mmol) in dry DMF (15 mL) under an argon atmosphere was added potassium carbonate (1.28 g, 9.24 mmol). The resulting mixture was allowed to stir at room temperature for 24 h, then diluted with EtOAc and filtered. The filtrate was washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 2 : 1 hexanes/ EtOAc to afford the title compound (578 mg, 74%) as a colorless oil which solidified upon standing. m.p. 58 - 59°C
^{1}H NMR ($CDCl_3$) : δ 8.60 (m, 1H); 8.00 (d, 1H); 7.72 (m, 1H); 7.50 (m, 1H); 7.21 (m, 1H); 6.90 (dd, 1H); 6.80 (d, 1H); 5.25 (s, 2H); 2.91 (t, 2H); 2.60 (t, 2H); 2.10 (m, 2H).
CIMS (NH_3), m/e : 271 [$(M+NH_4)^+$], 254 [$(M+H)^+$].
Anal. Calc. for $C_{16}H_{15}NO_2$: C 75.87, H 5.97, N 5.53; found : C 75.95, H 5.99, N 5.61.

b) 6-(2-Pyridinylmethoxy)-1-tetralone oxime. To a solution of 6-(2-pyridinylmethoxy)-1-tetralone (560 mg, 2.21 mmol) in dry pyridine (6 mL) under an argon atmosphere was added hydroxylamine hydrochloride (307 mg, 4.42 mmol). The resulting mixture was

heated at 50°C for 0.5 h, then allowed to cool to room temperature and concentrated under reduced pressure. The residue was crystallized from EtOH to afford the title compound as a white solid (468 mg, 79%). m.p. 164 - 165°C

^{1}H NMR ($CDCl_3$) : δ 8.60 (br d, 1H); 7.86 (d, 1H); 7.72 (m, 1H); 7.55 (apparent d, 1H); 7.26 (m, 1H); 6.86 (dd, 1H); 6.79 (d, 1H); 5.30 (s, 2H); 2.85 - 2.70 (overlapping t and m, 4H); 1.90 (m, 2H).

CIMS (NH_3), m/e : 286 [$(M+NH_4)^+$], 269 [$(M+H)^+$].

Anal. Calc. for $C_{16}H_{16}N_2O_2$: C 71.62, H 6.01, N 10.44; found : C 71.61, H 5.95, N 10.54:

c) N-1-[6-(2-Pyridinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine. To a solution of 6-(2-pyridinylmethoxy)-1-tetralone, oxime (335 mg, 1.25 mmol) in 2 : 1 Et_2O/ MeOH (65 mL) under an argon atmosphere at 0°C was added BH_3·pyridine (0.55 mL, 5.49 mmol). The reaction mixture was allowed to warm to room temperature. After stirring for 1 h, 2 N HCl (2 mL, 4.0 mmol) was added dropwise over 10 min. The mixture was stirred an additional 5 h, at which time 1 N HCl was added, and stirring was continued until the effervescence ceased. The pH was then adjusted to pH 9 - 10 by the addition of 3 N NaOH. The mixture was extracted with CH_2Cl_2 (4x), and the combined organic extracts were washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 2% MeOH/ CH_2Cl_2 to afford the hydroxyamine as a white solid (216 mg, 64%). m.p. 114 - 115°C

^{1}H NMR ($CDCl_3$) : δ 8.58 (br d, 1H); 7.70 (apparent t, 1H); 7.50 (d, 1H); 7.22 (m, 2H); 6.79 (dd, 1H); 6.71 (br s, 1H); 5.14 (s, 2H); 4.06 (m, 1H); 2.72 (m, 2H); 2.20 (m, 1H); 1.97 - 1.65 (m, 3H).

CIMS (NH_3), m/e : 271 [$(M+H)^+$], 253.

Anal. Calc. for $C_{16}H_{18}N_2O_2 \cdot 0.25\ H_2O$: C 69.92, H 6.78, N 10.19; found : C 70.24, H 6.86, N 10.30.

d) N-1-[6-(2-Pyridinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea. To a solution of N-1-[6-(2-pyridinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine (260 mg, 0.96 mmol) in dry THF (15 mL) under an argon atmosphere was added trimethylsilyl isocyanate (0.26 mL, 1.92 mmol). The resulting mixture was heated at 60°C for 1 h, then allowed to cool to room temperature and stirred an additional 1 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the solid residue was recrystallized from EtOH/ Et_2O to afford the title compound as an off-white solid (117 mg, 39%). m.p. 175 - 176°C

^{1}H NMR (DMSO-d$_6$) : δ 8.88 (s, 1H); 8.56 (d, 1H); 7.80 (t, 1H); 7.49 (d, 1H); 7.32 (m, 1H); 7.06 (d, 1H); 6.79 (dd, 1H); 6.71 (d, 1H); 6.30 (s, 2H); 5.22 (m, 1H); 5.12 (s, 2H); 2.54 (m, 2H); 2.00 - 1.57 (m, 4H).
IR (KBr) : 1675 cm^{-1}.
CIMS (NH_3), m/e : 331 [$(M+NH_4)^+$], 314 [$(M+H)^+$].
Anal. Calc. for $C_{17}H_{19}N_3O_3$: C 65.16, H 6.11, N 13.41; found : C 65.16, H 6.18, N 13.04.

Example 21

N-1-[6-(2-Benzimidazolylmethoxy)-(1,2,3,4-tetrahydronaphthyl)]-N-hydroxyurea

a) 6-(2-Benzimidazolylmethoxy)-1-tetralone. To a solution containing 6-hydroxy-1-tetralone (2.0 g, 12.3 mmol) and 2-(chloromethyl)benzimidazole (2.26 g, 13.6 mmol) in dry DMF (60 mL) under an argon atmosphere was added potassium carbonate (5.11 g, 37.0 mmol). The resulting mixture was allowed to stir at room temperature for 24 h, then diluted with EtOAc and filtered. The filtrate was washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 1 : 1 EtOAc/ hexanes to provide the title compound as a pale yellow solid (507 mg, 14%). m.p. 165 - 166°C
^{1}H NMR ($CDCl_3$) : δ 7.95 (d, 1H); 7.75 (br s, 1H); 7.45 (br s, 1H); 7.28 (m, 2H); 6.85 (dd, 1H); 6.75 (d, 1H); 5.40 (s, 2H); 2.88 (m, 2H); 2.60 (m, 2H); 2.10 (m, 2H).
Anal. Calc. for $C_{18}H_{16}N_2O_2$: C 73.95, H 5.52, N 9.58; found : C 73.48, H 5.51, N 9.55.

b) 6-(2-Benzimidazolylmethoxy)-1-tetralone, oxime. To a solution of 6-(2-benzimidazolylmethoxy)-1-tetralone (375 mg, 1.28 mmol) in pyridine (4 mL) was added hydroxylamine hydrochloride (178 mg, 2.56 mmol). The resulting mixture was heated at 50°C for 30 min, then allowed to cool to room temperature and concentrated under reduced pressure. The residue was crystallized from EtOH to provide the title compound as a white solid (278 mg, 71%). m.p. >210°C (dec)
^{1}H NMR ($CDCl_3$, MeOH-d$_4$) : δ 7.69 (d, 1H); 7.53 (m, 2H); 7.35 (m, 2H); 6.73 (m, 2H); 5.40 (s, 2H); 2.57 (m, 4H); 1.65 (m, 2H).
Anal. Calc. for $C_{18}H_{17}N_3O_2 \cdot HCl$: C 62.88, H 5.28, N 12.22; found : C 62.63, H 5.31, N 12.10

c) N-1-[6-(2-Benzimidazolylmethoxy)-(1,2,3,4-tetrahydronaphthyl)]-N-hydroxyamine. To a solution of 6-(2-benzimidazolylmethoxy)-1-tetralone, oxime (262 mg, 0.85 mmol) in 1 : 2 MeOH/ Et_2O (50 mL) at 0°C under an argon atmosphere was added BH_3·pyridine (0.38

mL, 3.75 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 1 h, at which time 2 N HCl (1.36 mL, 2.73 mmol) was added dropwise over 10 min. The resulting mixture was allowed to stir at room temperature overnight. To the mixture was added 1 N HCl, and stirring was continued until the effervescence ceased. The pH was adjusted to pH 9 - 10 by the addition of 3N NaOH, and the mixture was extracted with CH_2Cl_2 (4x). The combined organic extracts were washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the solid residue was recrystallized from CH_2Cl_2 to afford the title compound (129 mg, 49%). m.p. 157 - 159°C

^{1}H NMR (DMSO-d_6) : δ 7.60 (m, 1H); 7.47 (m, 1H); 7.32 - 7.12 (m, 3H); 6.83 (m, 2H); 5.22 (s, 2H); 3.80 (m, 1H); 2.65 (m, 2H); 2.04 (m, 2H); 1.88 (m, 1H); 1.60 (m, 2H).

d) N-1-[6-(2-Benzimidazolylmethoxy)-(1,2,3,4-tetrahydronaphthyl)]-N-hydroxyurea. To a solution of N-1-[6-(2-benzimidazolylmethoxy)-(1,2,3,4-tetrahydronaphthyl)]-N-hydroxyamine (115 mg, 0.37 mmol) in dry THF (7 mL) under an argon atmosphere was added trimethylsilyl isocyanate (0.10 mL, 0.74 mmol). The resulting mixture was heated at 60°C for 2 h, then allowed to cool to room temperature and concentrated under reduced pressure. The solid residue was purified by flash chromatography, eluting with 1 : 1 MeOH/ CH_2Cl_2 to afford the title compound as a white solid (64 mg, 49%). m.p. 158 - 161°C

^{1}H NMR (DMSO-d_6) : δ 8.88 (br s, 1H); 7.60 (m, 1H); 7.50 (m, 1H); 7.19 (m, 2H); 7.10 (br d, 1H); 6.85 (br dd, 1H); 6.78 (br d, 1H); 6.31 (br s, 2H); 5.23 (overlapping s and m, 3H); 2.63 (m, 2H); 2.00 - 1.77 (two overlapping m, 3H); 1.65 (m, 1H).

FAB MS, m/e : 391 [$(M+K)^+$], 375 [$(M+Na)^+$], 353 [$(M+H)^+$].

Anal. Calc. for $C_{19}H_{20}N_4O_3 \cdot H_2O$: C 61.61, H 5.99, N 15.13; found : C 61.71, H 5.98, N 14.84.

Example 22

N-1-(7-Phenoxyindanyl)-N-hydroxyurea

a) 7-Phenoxy-1-indanone, oxime. To a solution of 7-phenoxy-1-indanone (485 mg, 2.16 mmol, see example 18 for preparation) in pyridine (20 mL) was added hydroxylamine hydrochloride (300 mg, 4.32 mmol). The resulting mixture was heated at 50°C for 1 h and then allowed to cool. The mixture was concentrated under reduced pressure, and the residue was triturated with H_2O. The solid which formed was collected by filtration,

washed with H_2O and dried under reduced pressure to afford the oxime (460 mg, 89%) as a yellow solid. m.p. >200°C (dec)

b) N-1-(7-Phenoxyindanyl)-N-hydroxyamine. To a solution of 7-phenoxy-1-indanone, oxime (450 mg, 1.88 mmol) in 2 : 1 Et_2O/ MeOH (100 mL) under an argon atmosphere was added BH_3·pyridine (0.83 mL, 8.27 mmol), followed by the dropwise addition of 2 N HCl (3 mL, 6 mmol). The resulting mixture was allowed to stir at room temperature for 2 h, at which time 2 N HCl (20 mL) was added dropwise. The pH was adjusted to pH 9 - 10 by the addition of 3 N NaOH. The mixture was extracted with CH_2Cl_2 (4 x 100 mL), and the combined organic extracts were washed successively with H_2O and saturated aqueous and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 25% EtOAc/ hexanes to afford the title compound as a light brown oil which solidified upon standing (341 mg, 75%). The oil was triturated with cyclohexane providing a light tan solid.

c) N-1-(7-Phenoxyindanyl)-N-hydroxyurea. To a solution of N-1-(7-phenoxyindanyl)-N-hydroxyamine (315 mg, 1.30 mmol) in THF (20 mL) under an argon atmosphere was added trimethylsilyl isocyanate (0.35 mL, 2.60 mmol). The resulting mixture was heated to 60°C for 2 h, and then allowed to cool. The mixture was concentrated under reduced pressure, and the solid residue was recrystallized from EtOH to afford a tan solid. This was further purified by flash chromatography, eluting with 1 : 1 EtOAc/ hexanes to afford the title compound as a white solid (168 mg, 45%). m.p. 161 - 162°C
FAB MS, m/e : 285 [$(M+H)^+$].
Anal. Calc. for $C_{16}H_{16}N_2O_3 \cdot 1/8\ H_2O$: C 67.06, H 5.70, N 9.79; found : C 67.02, H 5.62, N 9.60.

Example 23
N-Hydroxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]acetamide

a) N-Acetoxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]acetamide. To a solution of N-hydroxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]amine (0.63 g, 2.4 mmol) in CH_2Cl_2 (12 mL) prepared in Example 8, Step (c) was added triethylamine (0.99 mL, 7.08 mmol) and acetyl chloride (0.37 mL, 5.19 mmol). The resulting mixture was stirred at room temperature for 30 min, then poured into dilute aqueous HCl and washed successively with H_2O and saturated aqueous NaCl. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with CH_2Cl_2 to provide the desired product (0.59 g, 72%).

b) N-Hydroxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]acetamide. To a solution of N-acetoxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]acetamide (590 mg, 1.7 mmol) in 2 : 1 isopropanol/ H_2O (6 mL) was added LiOH (204 mg, 8.5 mmol). The resulting mixture was stirred at room temperature for 30 min, then poured into CH_2Cl_2, washed successively with H_2O and saturated aqueous NaCl and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was recrystallized from CH_2Cl_2/ hexanes. The residue was further purified by flash chromatography, eluting with 25% EtOAc/ hexanes to provide the desired acetamide (67 mg, 13%).

250 MHz ^{1}H NMR ($CDCl_3$) : δ 5.80 and 5.10 (br t and dd, 1H); 2.87 (s, 4H); 2.76 (m, 2H); 2.25 (s, 3H); 2.06 (m, 3H); 1.81 (m, 1H).

IR (cm^{-1}) : 3090 - 3010, 2960 - 2780, 1620 - 1570.

CIMS (NH_3), m/e (rel. int.) : 310 [$(M+H)^+$, 4]; 294 (40), 235 (100).

Anal. Calc. for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53; found : C 77.55, H 7.34, N 4.51.

Example 24

N-Hydroxy-N-[1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)]acetamide

N-Hydroxy-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)]acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 1, step (d).

Example 25

N-Hydroxy-N-[1-(5-benzyloxyindanyl)]acetamide

N-Hydroxy-N-1-(5-benzyloxyindanyl)acetamide. The desired compound is prepared according to the method of Example 23 steps (a) and (b) except using a solution of N-1-(5-benzyloxyindanyl)-N-hydroxyamine as prepared in Example 2, step (d).

Example 26

N-Hydroxy-N-1-(6-methoxy-1,2,3,4-tetrahydronaphthyl)acetamide

N-Hydroxy-N-1-(6-methoxy-1,2,3,4-tetrahydronaphthyl)acetamide

The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-(6-methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 3, step (b).

Example 27

N-Hydroxy-N-1-(1,2,3,4-tetrahydronaphthyl)acetamide

N-Hydroxy-N-1-(1,2,3,4-tetrahydronaphthyl)acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-(1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 4, step (b).

Example 28

N-Hydroxy-N-1-[6-(4-methoxybenzyl)oxy-1,2,3,4-tetrahydronaphthyl]acetamide

N-Hydroxy-N-1-[6-(4-methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-[6-(4-methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine as prepared in Example 5, step (c).

Example 29

N-Hydroxy-N-1-[6-(4-chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]acetamide

N-Hydroxy-N-1-[6-(4-chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-[6-(4-chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine as prepared in Example 6, step (c).

Example 30

N-Hydroxy-N-1-[6-(2-naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]acetamide

N-Hydroxy-N-1-[6-(2-naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-[6-(2-naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine as prepared in Example 7, step (c).

Example 31

N-Hydroxy-N-3-(6-benzyloxy-2,3-dihydrobenzofuranyl)acetamide

N-Hydroxy-N-3-(6-benzyloxy-2,3-dihydrobenzofuranyl)acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-3-(6-benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine as prepared in Example 10, step (e).

Example 32

N-Hydroxy-N-1-[6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]acetamide

N-Hydroxy-N-1-[6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-[6-(2-quinolinylmethyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine as prepared in Example 9, step (c).

Example 33

N-Hydroxy-N-2-(7-methoxy-1,2,3,4-tetrahydronaphthyl)acetamide

N-Hydroxy-N-2-(7-methoxy-1,2,3,4-tetrahydronaphthyl)acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-2-(7-methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 11, step (b).

Example 34

N-Hydroxy-N-1-(7-benzyloxy-1,2,3,4-tetrahydronaphthyl)acetamide

N-Hydroxy-N-1-(7-benzyloxy-1,2,3,4-tetrahydronaphthyl)acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-(7-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 12, step (d).

Example 35

N-Hydroxy-N-[1-(6-phenyl-1,2,3,4-tetrahydronaphthyl)]acetamide

N-Hydroxy-N-[1-(6-phenyl-1,2,3,4-tetrahydronaphthyl)]acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-(6-phenyl-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 13, step (c).

Example 36

N-Hydroxy-N-1-[5-(4-methoxybenzyloxy)indanyl]acetamide

N-Hydroxy-N-1-[5-(4-methoxybenzyloxy)indanyl]acetamide The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution

of N-1-[5-(4-methoxybenzyloxy)indanyl]-N-hydroxyamine as prepared in Example 14, step (c).

Example 37

N-Hydroxy-N-3-[6-(4-methoxybenzyloxy)-2,3-dihydrobenzofuranyl]acetamide

N-Hydroxy-N-3-[6-(4-methoxybenzyloxy)-2,3-dihydrobenzofuranyl]acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-3-[6-(4-methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine as prepared in Example 15, step (c).

Example 38

N-Hydroxy-N-1-(5-benzyloxy-1,2,3,4-tetrahydronaphthyl)acetamide

N-Hydroxy-N-1-(5-benzyloxy-1,2,3,4-tetrahydronaphthyl)acetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-(5-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 16, step (c).

Example 39

N-Hydroxy-N-1-(6-phenoxy-1,2,3,4-tetrahydronaphthyl)]acetamide

a) 6-Phenoxy-1-tetralone. A solution of 6-(1-tetralonyl) trifluoromethylsulfonate (447 mg, 1.5 mmol; see example 1 for preparation) and phenol (300mg, 3.2 mmol) in dry collidine (3 mL) containing Cu_2O (107 mg,0.75 mmol) is heated at 170° C for 72 h. The resulting solution is diluted with ether, washed with 6N HCl and brine and then concentrated in vacuo to yield the desired biaryl ether.

b) 6-Phenoxy-1-tetralone oxime. To a solution of 6-phenoxy-1-tetralone (2.4 g, 10.7 mmol) in dry pyridine (25 mL) is added hydroxylamine hydrochloride (1.4 g, 24 mmol). The resulting mixture is heated at 50°C for 30 min, then allowed to cool and concentrated under reduced pressure to afford the oxime.

c) N-1-(6-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine. To a solution of the oxime prepared above (2.39 g, 10 mmol) in 2:1 Et_2O: MeOH (200 mL) at 0°C is added BH_3·pyridine complex (3.9 mL, 38 mmol). After warming to room temperature and stirring for 1 h, 6N HCl (5 mL) is added, and the reaction mixture is stirred an additional 2

h. At this time, more BH_3·pyridine (2 mL, 20 mmol) is added, followed by 6N HCl (30 mL) and the reaction is allowed to stir overnight. The reaction mixture is adjusted to pH 10 with 10% NaOH and extracted with Et_2O. The organic extract is washed successively with H_2O and saturated aqueous NaCl and concentrated *in vacuo* to yield the hydroxyamine which is used without further purification.

d) N-Hydroxy-N-1-(6-phenoxy-1,2,3,4-tetrahydronaphthyl)lacetamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of N-1-(6-phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in step (c) above.

Example 40

N-Hydroxy-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)propionamide

N-Hydroxy-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)propionamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of propionyl chloride and a solution of N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine as prepared in Example 1, step (d).

Example 41

N-Hydroxy-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthylbenzamide

N-Hydroxy-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthylbenzamide. The desired compound is prepared according to the method of Example 23, steps (a) and (b) except using a solution of benzyl chloride and a solution of N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl) -N-hydroxyamineas prepared in Example 1, step (c).

Example 42

N-Hydroxy-N-1-[6-(2-phenethyl)-1,2,3,4-tetrahydronaphthyl]-2,2-dimethylpropionamide

a) 1-Hydroxy-6-(2-phenethyl)-1,2,3,4-tetrahydronaphthalene. To a solution of 6-(2-phenethyl)-1-tetralone (see Example 8, step (b), 2.50 g, 10.0 mmol) in THF under an argon atmosphere is added lithium aluminum hydride (190 mg, 5.0 mmol). The resulting mixture is stirred at room temperature for several h and quenched by the successive dropwise addition of H_2O (0.19 mL), 15% NaOH (0.19 mL) and H_2O (0.57 mL). The alcohol is obtained by filtration and removal of the solvent *in vacuo*.

b) 1-Chloro-6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthalene. To a solution of 1-hydroxy-6-(2-phenethyl)-1,2,3,4-tetrahydronaphthalene (2.52 g, 10.0 mmol) in CH_2Cl_2 (15 mL) is

added CCl_4 (1.21 mL, 12.5 mmol). Triphenylphosphine (3.93 g, 15.0 mmol) is added portionwise with cooling, and the resulting mixture is allowed to warm to room temperature and stirred for 30 min. The solvent is removed *in vacuo*. Ether is added to the residue, which is washed with H_2O and dried. The desired product is obtained by removal of the solvent *in vacuo*.

c) N-Benzyloxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]amine. To a suspension of O-benzylhydroxylamine hydrochloride (4.79 g, 30.0 mmol) in THF (150 mL) is added triethylamine (4.20 mL, 30.0 mmol). After stirring for 1 h, at room temperature, the mixture is filtered and is concentrated under reduced pressure. The residue is dissolved in benzene (15 mL) and is added to a solution of 1-chloro-6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthalene (2.71 g, 10.0 mmol). The resulting mixture is stirred at room temperature for 48 h. The alkylated O-benzylhydroxylamine is obtained after removal of the solvent under reduced pressure and purification by flash chromatography.

d) N-Benzyloxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]-2,2-dimethylpropionamide. To a solution of N-benzyloxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]amine (3.57 g, 10.0 mmol) in THF is added triethylamine (1.72 mL, 12.5 mmol), followed by trimethylacetyl chloride (1.54 mL, 12.5 mmol). The resulting mixture is stirred at room temperature for 2 h and is filtered. The desired product is obtained by removal of the solvent *in vacuo*.

e) N-Hydroxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]-2,2-dimethylpropionamide. To a solution of N-benzyloxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]-2,2-dimethylpropionamide (4.41 g, 10.0 mmol) in absolute EtOH is added 5% palladium on activated carbon (0.25 mmol), and the mixture is hydrogenated at 25 psi H_2 for 24 h. The mixture is filtered, and the solvent is removed *in vacuo* to provide the N-hydroxyamide which is purified by flash chromatography.

Example 43

(+)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

and

(-)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea

(S)-4-Benzyl-2-oxazolidinone-N-3-carboxylic acid chloride. A dispersion of 60% sodium hydride in mineral oil (0.82 g of , 20.3 mmol) was washed with pentane. The pentane was replaced with dry toluene (70 mL), and to the resulting suspension was added (S)-4-benzyl-2-oxazolidinone (3.00 g, 16.9 mmol). The mixture was heated at reflux overnight, then

allowed to cool to -17°C and added slowly to a pre-cooled (-17°C) solution of phosgene (110 mL of 20% solution in toluene, 22.1 mmol). The resulting mixture was stirred at -17°C for 1 h, and then filtered and concentrated under reduced pressure. The residue was washed with hexanes to afford the title compound (2.91 g, 72%).
^{1}H NMR ($CDCl_3$) : δ 7.34 - 7.17 (m, 5H); 4.68 (m, 1H); 4.22 (m, 2H); 3.32 (dd, 1H); 2.91 (dd, 1H).
IR : 2150, 1830, 1800, 1725 cm^{-1}.

(1RS, 4S)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-(N'-4-benzyl-3-carboxyloxazolidin-2-onyl)urea. To a solution of N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea (2.00 g, 6.4 mmol) in CH_2Cl_2 (300 mL) was added triethylamine (1.7 mL, 12.8 mmol), followed by (S)-4-benzyl-2-oxazolidinone-N-3-carboxylic acid chloride (2.30 g, 9.6 mmol). The resulting mixture was stirred at room temperature for 1 h, then poured into $CHCl_3$ and washed successively with H_2O and saturated aqueous NaCl and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 2% MeOH/ CH_2Cl_2 to afford the title compound as a mixture of diastereomers (2.77 g, 84%). The diastereomers were separated by semi-preparative, reverse-phase HPLC (Ultrasphere column, 30 mL/ min flow rate, 280 nm UV detector), eluting with 7 : 3 DMF/H_2O.

(-)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea. To a solution of one of the diastereomers obtained from the separation of (1RS, 4S)-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-(N'-4-benzyl-3-carboxyloxazolidin-2-onyl)urea in 4 : 1 THF/ H_2O (21 mL) at 0°C was added hydrogen peroxide (40 mL of 30% aqueous solution), followed by lithium hydroxide (0.40 g, 9.5 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then cooled to 0°C, and saturated aqueous $NaHSO_3$ (50 mL) was slowly added. The mixture was extracted with EtOAc, and the organic extract was washed successively with H_2O and saturated aqueous NaCl and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 2% MeOH/ $CHCl_3$ to afford the title compound. This isomer was determined by HPLC analysis (eluting with 2 : 8 isopropanol/ hexanes, chiracel column, 254 nm uv detector) to consist of 98% enantiomeric excess. m.p. 146 - 147°C. $[\alpha]_D = -1.53°$.
^{1}H NMR (MeOH-d_4) : δ 7.48 (m, 5H); 7.18 (d, 1H); 6.80 (dd, 1H); 6.71 (d, 1H); 5.42 (apparent t, 1H); 5.04 (s, 2H); 2.90 - 2.63 (m, 2H); 2.02 (m, 3H); 1.78 (m, 1H).

(+)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea. The (+)-enantiomer was prepared in a similar fashion, except using the other diastereomer obtained from the

separation of (1RS, 4S)-N-1-(6-benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-(N'-4-benzyl-3-carboxyloxazolidin-2-onyl)urea. The (+) isomer was determined by HPLC (eluting with 2 : 8 isopropanol/ hexanes, chiracel column, 254 nm uv detector) analysis to consist of 88% enantiomeric excess. m.p. 154.5 - 155.5°C. $[\alpha]_D = +2.98°$.
^{1}H NMR (MeOH-d_4) : δ 7.37 (m, 5H); 7.20 (d, 1H); 6.80 (dd, 1H); 6.71 (d, 1H); 5.43 (apparent t, 1H); 5.05 (s, 2H); 2.90 - 2.63 (m, 2H); 2.00 (m, 3H); 1.78 (m, 1H).
IR : 3500, 3460, 3360, 3180 - 3100, 2940, 2880, 1650, 1635 cm^{-1}.

Example 44
(+)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea
and
(-)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea

(3RS, 4S)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-(N'-4-benzyl-3-carboxy-oxazolidin-2-onyl)urea. To a solution of N-3-(6-benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea (2.01 g, 6.41 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (1.7 mL, 12.8 mmol), followed by (S)-4-benzyl-2-oxazolidinone-N-3-carboxylic acid chloride (2.30 g, 9.6 mmol). The resulting mixture was stirred at room temperature for 1 h, then washed successively with H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 1% MeOH/ CH_2Cl_2 to afford the title compound as a mixture of diastereomers (1.67 g, 68%). The diastereomers were separated by normal-phase HPLC (porasil column, 400 mL/ min flow rate, R.I. detector), eluting with 60 : 40 : 1 hexanes/ EtOAc/ HCO_2H.

(+)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea. To a solution of one of the diastereomers obtained from the separation of (3RS, 4S)-N-3-(6-benzyloxy-2,3-dihydrobenzofuryl)-N-(N'-4-benzyl-3-carboxy-oxazolidin-2-onyl)urea in 3 : 1 THF/ H_2O (12 mL) at 0°C was added hydrogen peroxide (6.6 mL of 30% aqueous solution), followed by lithium hydroxide (0.07 g, 1.68 mmol). The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then cooled to 0°C, and saturated aqueous $NaHSO_3$ was slowly added. The mixture was concentrated under reduced pressure, and the residue was extracted with CH_2Cl_2. The organic extract was concentrated *in vacuo*, and the residue was purified by flash chromatography, eluting with 5% MeOH/ $CHCl_3$ to afford the title compound. This isomer was determined by HPLC analysis (eluting with 2 : 8 isopropanol/ hexanes, chiracel column, 254 nm uv detector) to consist of 97% enantiomeric excess. m.p. 189 - 190°C. $[\alpha]_D = +10.1°$ (DMSO).
^{1}H NMR (DMSO-d_6) : δ 9.12 (s, 1H); 7.40 (m, 5H); 7.05 (d, 1H); 6.50 (m, 4H); 5.78 (dd, 1H); 5.05 (s, 2H); 4.56 (apparent t, 1H); 4.45 (dd, 1H).

IR : 3480, 3340, 3200 - 3160, 2920 - 2880, 1650, 1635 cm^{-1}.
CIMS (NH_3), m/z (rel. int.) : 318 [$(M+NH_4)^+$, 11], 225 (100).
Anal. Calc. for $C_{16}H_{16}N_2O_4$: C 63.99, H 5.37, N 9.33; found : C 62.68, H 5.23, N 8.73.

(-)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea. The (-)-enantiomer was prepared in a similar fashion, except using the other diastereomer obtained from the separation of (3RS, 4S)-N-3-(6-benzyloxy-2,3-dihydrobenzofuryl)-N-(N'-4-benzyl-3-carboxy-oxazolidin-2-onyl)urea. m.p. 188 - 189°C. $[\alpha]_D$ = -10.7° (DMSO).
^{1}H NMR (DMSO-d_6) : δ 9.12 (s, 1H); 7.40 (m, 5H); 7.06 (d, 1H); 6.49 (m, 4H); 5.78 (dd, 1H); 5.05 (s, 2H); 4.56 (apparent t, 1H); 4.46 (dd, 1H).
IR : 3480, 3340, 3180, 2880, 1650, 1635 cm^{-1}.
CIMS (NH_3), m/z (rel. int.) : 318 [$(M+NH_4)^+$, 11], 225 (100).
Anal. Calc. for $C_{16}H_{16}N_2O_4$: C 63.99, H 5.37, N 9.33; found : C 63.76, H 5.24, N 9.20.

EXAMPLE 45 - CAPSULE COMPOSITION

A pharmaceutical composition of this invention in the form of a capsule is prepared by filling a standard two-piece hard gelatin capsule with 50 mg. of a compound of Formula (I), in powdered form, 110 mg. of lactose, 32 mg. of talc and 8 mg. of magnesium stearate.

EXAMPLE 46 - OINTMENT COMPOSITION

Compound of Formula (I) 1.0 g
White soft paraffin to 100.0 g

The compound of Formula (I) is dispersed in a small volume of the vehicle and this dispersion is gradually incorporated into the bulk to produce a smooth, homogeneous product which is filled into collapsible metal tubes.

EXAMPLE 47 - TOPICAL CREAM COMPOSITION

Compound of Formula (I) 1.0 g
Carbowax 200 20.0 g
Lanolin Anhydrous 2.0 g
White Beeswax 2.5 g
Methyl hydroxybenzoate 0.1 g
Distilled Water to 100.0 g

The carbowax, beeswax and lanolin are heated together at 60°C and added to a solution of methyl hydroxybenzoate. Homogenization is achieved using high speed stirring and the temperature is allowed to fall to 50°C. The compound of Formula (I) is

added and dispersed throughout, and the composition is allowed to cool with slow speed stirring.

EXAMPLE 48- TOPICAL LOTION COMPOSITION

Compound of Formula (I) 1.0 g
Sorbitan Monolaurate 0.6 g
Polysorbate 20 0.6 g
Cetostearyl Alcohol 1.2 g
Glycerin 6.0 g
Methyl Hydroxybenzoate 0.2 g
Purified Water B.P. to 100.00 ml

The methyl hydroxybenzoate and glycerin are dissolved in 70 ml of the water at 75°C. The sorbitan monolaurate, polysorbate 20 and cetostearyl alcohol are melted together at 75°C and added to the aqueous solution. The resulting emulsion is homogenized, allowed to cool with continuous stirring and the compound of Formula (I) is added as a suspension in the remaining water. The whole suspension is stirred until homogenized.

EXAMPLE 49 - COMPOSITION FOR ADMINISTRATION BY INHALATION

For an aerosol container with a capacity of 15-20 ml: Mix 10 mg of a compound of Formula (I) with 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and disperse such mixture in a propellant (c.a.), such as freon, preferably a combination of freon 114 and freon 12, and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

EXAMPLE 50 - COMPOSITION FOR ADMINISTRATION BY INHALATION

For an aerosol container with a capacity of 15-20 ml: Dissolve 10 mg of a compound of Formula (I) in ethanol (6-8 ml), add 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and disperse such in a propellant (c.a.), such as freon, preferably a combination of freon 144 and freon 12, and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

UTILITY EXAMPLES

I. METHODS

For the in vitro experiments, compounds were dissolved at appropriate concentrations in ethanol or DMSO (dimethylsulfoxide) having a final concentration of less than or equal to 1.0%, and then diluted to their respective concentrations using the buffers indicated in the text.

Animals:

In experiments when mice were used they were CD1 mice obtained from Charles River Breeding Laboratories, and within a single experiment the mice were age-matched. Their weight range was from 25 to 42 g. The test groups generally contained 3-6 animals.

5-LIPOXYGENASE ACTIVITY:

The 5-lipoxygenase (5-LO) was isolated from extracts of RBL-1 cells. The assay for assessing inhibition of the 5-LO activity was a continuous assay which monitored the comsumption of oxygen (O_2). The cell extract (100 ug) was preincubated with the inhibitor or its vehicle in 25 mM BisTris buffer (pH 7.0) that contained 1 mM EDTA, 1 mM ATP, 150 mM NaCl and 5% ethylene glycol for 2 minutes at 20°C (total volume 2.99 ml). Arachidonic acid (10 uM) and $CaCl_2$ (2 mM) were added to start the reaction, and the decrease in O_2 concentration followed with time using a Clark-type electrode and the Yellow Spring O_2 monitor (type 53) (Yellow Springs, OH). The optimum velocity was calculated from the progress curves. All compounds were dissolved in ethanol with the final concentration of ethanol being 1% in the assay.

Drug-induced effects on enzyme activities are described as the concentration of drug causing a 50% inhibition of oxygen consumption (IC_{50}).

EICOSANOID PRODUCTION FROM HUMAN MONOCYTES IN VITRO

Human monocytes were prepared from leukosource packs supplied by the American Red Cross. The leukosource packs were fractionated by a two-step procedure described by F. Colatta et al. (J. Immunology 132:936, 1984) that uses sedimentation on Ficoll followed by sedimentation on Percoll. The monocyte fraction that results from this technique was composed of 80-90% monocytes with the remainder being neutrophils and lymphocytes. In addition, significant number of platelets are present.

The monocytes (10^6 cells) were placed into polypropylene tubes and used as a suspended culture. The assay buffer consisted of RPMI 1640 buffer, 2 mM glutamine, 2.5 mM HEPES and 2 mM $CaCl_2$ (total volume 0.475 ml). Compounds (0.005 ml) were added in DMSO, and the cells were preincubated for 10 minutes at 37°C with constant agitation. A23187 (2 uM) was used to stimulate the cells. After an additional 10 minutes, the buffer was collected by centrifugation (2500 xg for 15 minutes), and stored at -70°C until assayed. LTB_4 production was measured by radioimmunassay which was performed according to the manufacturer's (Advanced Magnetics, Boston, MA) instructions. PGE_2 was determined using an RIA kit supplied by New England Nuclear (Boston, MA).

EX VIVO MOUSE BLOOD EICOSANOID ASSAY

Mice were pre-treated per os with vehicle or a test compound (dissolved in dimethylacetamide and diluted 1 to 10 with sesame oil) 30 minutes prior to removal of blood. The 5-lipoxygenase product LTB_4, was extracted from whole blood following A23187 stimulation. Aliquots of pooled heparinized mouse blood (1 ml each aliquot) from male CD1 mice (Charles River) were placed into 4 ml polypropylene tubes. The tubes were preincubated for about five minutes at 37°C. A23187 (60 uM) was added to stimulate eicosanoid production. Several aliquots of blood were not stimulated and, thus, provided background levels for eicosanoid production. All tubes were incubated for about 30 minutes at 37°C. The blood samples were centrifuged at 400 xg for about 15 minutes, and the plasma recovered for extraction. One volume of chilled acetonitrile was added to all at 5°C. The supernatants were recovered and diluted with 1% formic acid:1% triethylamine to achieve a final concentration of 20% acetonitrile. These supernatants were then loaded onto the extraction cartridge that had been conditioned according to the Manufacturer's instructions (Solid Phase Extraction Columns, J. T. Baker, C18 3 ml size). The samples were washed with 3 ml of 1% formic acid:1% triethylamine, air dried, and then washed with 3 ml of petroleum ether. After air drying again, the samples were eluted with methyl formate. The eluents were concentrated under vacuum. The concentrates were resuspended in 30% acetonitrile buffered with 50 mM ammonium acetate (200 ul). The recovery of LTB_4 was 60%. The 300 ul concentrates were assayed by radioreceptor assay for LTB_4 by labortatory protocol.

PHENYLBENZOQUINONE-INDUCED ABDOMINAL CONSTRICTION ASSAY

Phenylbenzoquinone (PBQ, Eastman Kodak Co., Rochester, NY) was dissolved in warm (50°C) ethanol and diluted with distilled water to a final concentration of 0.2 mg/ml. The solution which was protected from light by a foil wrap was administered intraperitoneally at a dose volume of 0.01 ml/gm.

Mice were pre-treated with vehicle or test compound (dissolved or suspended in 25% PEG 200) for about 15 minutes and then injected with PBQ, following which each mouse was placed into individual 4 liter beakers. CD1 mice show a characteristic abdominal contraction/stretching response which consists of extending one or both of the hind limbs. These responses which occur at a variable frequency (not less than 1-2 seconds apart) were counted on a hand counter. The counting period was for 10 minutes following a 5 minute acclimation period. Results are based on the total number of constrictions observed during the 10 minute period.

DATA ANALYSIS AND STATISTICS

Mean values for groups were calculated and percent inhibition was determined between the vehicle control mean and test group. The ED_{50} was determined using linear regression analysis and was taken as the dose which resulted in a 50% inhibition of the vehicle control constriction response. Statistical analysis was done using Student's "t" test and a $p<0.05$ was considered statistically significant.

RESULTS

The effect of hydroxyurea compounds as inhibitors of 5-LO is shown in Table I. The compounds tested displayed a range of inhibitory activity both in vitro and in vivo. On the RBL-1 supernatant 5-LO enzyme assay several compounds showed activity in and around 1.0 uM IC_{50}. A second group of compounds had activity in the range of 2-3 uM IC_{50} and a third group had appreciably less activity (15-48 uM IC_{50}), which can be seen from a review of Table 1. Examination of the activity of the first two groups of compounds on human monocyte production of LTB_4 corroborated the 5-LO inhibitory activity. All the compounds tested were less than 1 uM IC_{50}. In contrast, none of the compounds showed potent inhibition of cyclooxygenase activity as indicated by production of the prostaglandin, PGE_2.

Evaluation of the in vivo 5-LO inhibitory activity of these compounds was done using mouse whole blood stimulated with calcium ionophore (A23187) ex vivo. As seen in Table II, with the exception of three compounds (3, 7 and 12) all of the others tested were shown to inhibit 5-LO activity ex vivo as well as in vitro. Several of these compounds also showed dose-related inhibition of LTB_4 production (ED_{50}'s ranged from 1-10 mg/kg, p.o.).

N-Acetoxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]acetamide, showed a 64 percent inhibition of LTB_4 in mouse blood ex vivo at a dose of 10mg/kg, or an IC_{50} of 5.8. Compounds of Formula (II): N-1-(5-Benzyloxyindanyl)-N-hydroxyamine, N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine, N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine, N-1-(5-Phenoxyindanyl)-N-hydroxyamine all inhibited LTB_4 at a dose of 10mg/kg.

The analgetic activity of these compounds was tested using the phenylbenzoquinone-induced abdominal constriction assay. As seen in Table II, several of these compounds (1, 2, 5, 6,7, 8 and 10) possessed significant analgetic activity. Several of these compounds also showed a dose response (ED_{50} 7.9 to 11.2 mg/kg, p.o.).

N-Acetoxy-N-1-[6-(2-phenylethyl)-1,2,3,4-tetrahydronaphthyl]-acetamide, a hydroxamate of Formula (I) compounds yielded a statistically significant percent inhibition of PBQ writhing at a dose of 10mg/kg of 27%. Compounds of Formula (II): N-1-(5-Benzyloxyindanyl)-N-hydroxyamine yielded a statistically significant percent inhibition of

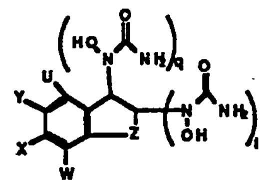
PBQ writhing at a dose of 10mg/kg; N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine, N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine, N-1-(5-Phenoxyindanyl)-N-hydroxyamine, yielded a statistically significant percent inhibition of PBQ writhing at a dose of 20mg/kg.

Discussion and Conclusion

The compounds shown herein inhibited 5-LO enzyme activity using isolated enzyme, whole cells and mouse blood, ex vivo. This inhibition of fatty acid oxygenase activity did not extend to cyclooxygenase and therefore, these selective 5-LO inhibitors would not be expected to have analgetic activity which is a property of cyclooxygenase inhibitors (Doherty, N.S. Mediators of the Pain of Inflammation. Annual Reports in Med. Chem. 22: 245-252, 1987). It was therefore surprising to find that many of these 5-LO inhibitors had significant and potent analgetic activity. This property enhances the utility of these inhibitors in diseases such as osteoarthritis were the clinical endpoint is pain (Moskowitz, R.W. Treatment of Osteoarthritis. In: Arthritis and Allied Conditions. Ed. D.J. McCarty. Lea and Febiger, Philadelphia, PA p.1181-1189, 1979).

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

TABLE I

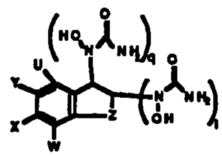


example	X	q\l	Y	W	U	Z	5-LO IC_{50}, μM	Human Monocytes IC_{50}, μM LTB_4	PGE_2
1	OCH_2Ph	1\0	H	H	H	$(CH_2)_2$	1.8	0.19	>30
2	OCH_2Ph	1\0	H	H	H	CH_2	1.5	0.19	NT
3	OCH_3	1\0	H	H	H	$(CH_2)_2$	48.0	NT	NT
4	H	1\0	H	H	H	$(CH_2)_2$	29.0	NT	NT
5	OCH_2(4-OMe-Ph)	1\0	H	H	H	$(CH_2)_2$	0.5	0.15	NT
6	OCH_2(4-Cl-Ph)	1\0	H	H	H	$(CH_2)_2$	2.2	0.32	NT
7	OCH_2(2-naphthyl)	1\0	H	H	H	$(CH_2)_2$	0.5	0.25	stim
8	$(CH_2)_2Ph$	1\0	H	H	H	$(CH_2)_2$	0.6	0.02	stim
9	OCH_2(2-quinolyl)	1\0	H	H	H	$(CH_2)_2$	1.9	0.09	>30
10	OCH_2Ph	1\0	H	H	H	O	2.3	0.42	>30
11	H	0\1	OCH_3	H	H	$(CH_2)_2$	15.0	NT	NT
12	H	1\0	OCH_2Ph	H	H	$(CH_2)_2$	3.0	0.74	>30
13	Ph	1\0	H	H	H	$(CH_2)_2$	1.5	0.34	>30
14	OCH_2(4-OMe-Ph)	1\0	H	H	H	CH_2	1.4	0.33	>30
15	OCH_2(4-OMe-Ph)	1\0	H	H	H	O	2.7	0.75	>30
16	H	1\0	H	OCH_2Ph	H	$(CH_2)_2$	0.91	0.16	>30
17	H	1\0	H	OPh	H	$(CH_2)_2$	0.84	0.12	>30
18	OPh	1\0	H	H	H	CH_2	0.85	0.33	>30
19	H	1\0	H	O(4-F-Ph)	H	$(CH_2)_2$	0.61	0.45	>30
20	OCH_2(2-pyridyl)	1\0	H	H	H	$(CH_2)_2$	10	NT	NT
21	OCH_2(2-benzimidazole)	1\0	H	H	H	$(CH_2)_2$	11	NT	NT
22	H	1\0	H	H	OPh	CH_2	5.6	NT	NT

NT - not tested

stim - stimulated above control values

TABLE II



example	X	q\l	Y	W	U	Z	% inh.of LTB_4 mouse blood ex vivo @ 10 mg/kg (ED_{50})	% inh. PBQ writhing @ 10mg/kg(ED_{50})
1	OCH_2Ph	1\0	H	H	H	$(CH_2)_2$	67 (9.9 mg/kg)	58 (7.9)
2	OCH_2Ph	1\0	H	H	H	CH_2	85 (4.0 mg/kg)	52 (7.7)
3	OCH_3	1\0	H	H	H	$(CH_2)_2$	NA	NA
4	H	1\0	H	H	H	$(CH_2)_2$	30	NA
5	OCH_2(4-OMe-Ph)	1\0	H	H	H	$(CH_2)_2$	81 (4.8 mg/kg)	68 (10.2)
6	OCH_2(4-Cl-Ph)	1\0	H	H	H	$(CH_2)_2$	70 (4.5 mg/kg)	72 (11.2)
7	OCH_2(2-naphthyl)	1\0	H	H	H	$(CH_2)_2$	19@ 10 mg/kg	23
8	$(CH_2)_2Ph$	1\0	H	H	H	$(CH_2)_2$	34	56 (8.9)
9	OCH_2(2-quinolyl)	1\0	H	H	H	$(CH_2)_2$	65 (10.2 mg/kg)	NA (62 % @ 2 &3 h @ 20)
10	OCH_2Ph	1\0	H	H	H	O	100 (3.9)	38 (7.7)
11	H	0\1	OCH_3	H	H	$(CH_2)_2$	NT	NA
12	H	1\0	OCH_2Ph	H	H	$(CH_2)_2$	STIM (59-100)	23%@ 20 mg/kg
13	Ph	1\0	H	H	H	$(CH_2)_2$	52	NA
14	OCH_2(4-OMe-Ph)	1\0	H	H	H	CH_2	10	NT
15	OCH_2(4-OMe-Ph)	1\0	H	H	H	O	73(9.8)	NA
16	H	1\0	H	OCH_2Ph	H	$(CH_2)_2$	44 (>15)	64% @ 20 mg/kg
17	H	1\0	H	OPh	H	$(CH_2)_2$	57	NA (11% @ 20 mg/kg)
18	OPh	1\0	H	H	H	CH_2	88 (6.4)	NA (8% @ 20 mg/kg)
19	H	1\0	H	O(4-F-Ph)	H	$(CH_2)_2$	85	32 % @ 20 mg/kg
20	OCH_2(2-pyridyl)	1\0	H	H	H	$(CH_2)_2$	NT	NT
21	OCH_2(2-benzimidazole)	1\0	H	H	H	$(CH_2)_2$	NT	NT
22	H	1\0	H	H	OPh	CH_2	NT	NT

NA - not active

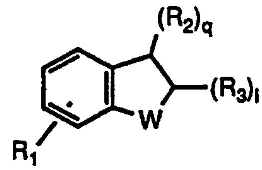
NT - not tested

Stim - stimulated above controls

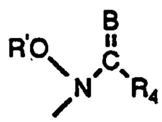
values given in parentheses represent the ED50 in mg/kg

What is claimed is:

1. A compound of the formula



wherein

R_2 and R_3 are  ;

R' is hydrogen, a pharmaceutically acceptable cation, aroyl or a C_{1-12} alkoyl;

B is oxygen or sulfur;

R_4 is NR_5R_6, alkyl $_{1-6}$, halosubstituted alkyl $_{1-6}$, hydroxy substituted alkyl $_{1-6}$, alkenyl $_{2-6}$, aryl or heteroaryl optionally substituted by halogen, alkyl $_{1-6}$, halosubstituted alkyl$_{1-6}$, hydroxyl, or alkoxy $_{1-6}$;

R_5 is H or alkyl$_{1-6}$;

R_6 is H, alkyl$_{1-6}$, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl$_{1-12}$, alkoxy $_{1-6}$, halosubstituted alkyl$_{1-6}$, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R_5 and R_6 may together form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen;

W is $CH_2(CH_2)_s$, $O(CH_2)_s$, $S(CH_2)_s$, or $NR_7(CH_2)_s$;

R_7 is hydrogen, C_{1-4} alkyl, phenyl, C_{1-6} alkoyl, or aroyl;

s is a number having a value of 0 to 3; provided that when l is one and W is $O(CH_2)_s$, $S(CH_2)_s$, then s is 1 to 3; and when W is $NR_7(CH_2)_s$ then s is 1 to 3 and q is 1;

q is a number having a value of 0 or 1;

l is a number having a value of 0 or 1;

provided that when q is 0 then l is 1 and R_2 is hydrogen; and when q is 1 then l is 0 and R_3 is hydrogen;

R_1 is a member selected from the group consisting of hydrogen, alkyl$_{1-10}$, alkoxy$_{1-10}$, $(CH_2)_m$-Ar-$(X)_v$, $O(CH_2)_m$Ar-$(X)_v$, or $S(CH_2)_m$-Ar-$(X)_v$;

m is a number having a value of 0 to 3;

v is a number having a value of 0 to 3;

Ar is a member selected from the group consisting of phenyl, napthyl, quinolyl, isoquinolyl, pyridyl, furanyl, imidazoyl, benzimidazoyl, triazolyl, oxazolyl, isoxazolyl, thiazole, or thienyl;

X is a member selected from the group consisting of hydrogen, halogen, alkyl $_{1-5}$, cycloalkyl $_{5-8}$, hydroxy, $(CHY)_t$carboxy, O-alkyl $_{1-5}$, $S(O)_r$ alkyl $_{1-5}$, halosubstituted alkyl$_{1-6}$, $(CHY)_tN(R_5)_2$ or cyano; provided that if v is a number greater than 1 then one substituent must be selected from alkyl, O-alkyl $_{1-5}$, or halo;
r is a number having a value of 0 to 2;
Y is hydrogen or alkyl$_{1-3}$;
t is a number having a value of 0 or 1; provided that when q is 1, R_4 is NR_4R_5, W is $CH_2(CH2)_s$, and s is 1, then R_1 is other than hydrogen, alkyl$_{1-10}$, or alkoxy $_{1-10}$;
and the pharmaceutically acceptable salts thereof.

2. The compound according to Claim 1 wherein W is $CH_2(CH_2)_s$ or $O(CH_2)_s$, and s is a number having a value of 0 or 1.

3. The compound according to Claim 2 wherein R_4 is alkyl $_{1-6}$, halosubstituted alkyl $_{1-6}$, hydroxy substituted alkyl $_{1-6}$, alkenyl $_{2-6}$, aryl or heteroaryl optionally substituted by halogen, alkyl $_{1-6}$, halosubstituted alkyl$_{1-6}$, hydroxyl, or alkoxy $_{1-6}$.

4. The compound according to Claim 2 wherein R_4 is NR_5R_6.

5. The compound according to Claim 3 wherein B is oxygen and q is 1.

6. The compound according to Claim 5 wherein R_1 is $O(CH2)_m$-Ar-$(X)_v$, $(CH2)_m$-Ar-$(X)_v$, or $S(CH2)_m$-Ar-$(X)_v$; m is a number having a value of 0 to 2; and v is a number having a value of 1 to 2.

7. The compound according to Claim 6 wherein s is 1,W is CH_2CH_2, R_1 is in the 5- or 6-position; and when W is OCH_2, R_1 is in the 7- or 8-position; and when s is 0, W is CH_2, R_1 is in the 4- or 5-position, and when W is O, R_1 is in the 6- or 7-position.

8. The compound according to Claim 7 wherein R_1 is benzyloxy, 4-methoxybenzyloxy, 4-chlorobenzyloxy, phenoxy, or 4-flurophenoxy.

9. The compound according to Claim 8 wherein R_5 and R_6.are independently selected from hydrogen or alkyl.

10. The compound according to Claim 1 wherein the compound and their pharmaceutically acceptable salts are selected from
N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;

N-1-(5-Benzyloxyindanyl)-N-hydroxyurea;
N-1-(6-Methoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(1,2,3,4-Tetrahydronaphthyl)-N-hydroxyurea;
N-1-[6-(4-Methoxybenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(4-Chlorobenzyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Naphthylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Phenethyl)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Quinolinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-3-(6-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyurea;
N-1-(7-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(6-Phenyl-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-[5-(4-methoxybenzyloxy)-indanyl]-N-hydroxyurea;
N-3-[6-(4-Methoxybenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea;
N-1-(5-Phenoxyindanyl)-N-hydroxyurea;
N-1-(4-Phenoxyindanyl)-N-hydroxyurea;
N-1-(5-(4-Flurophenoxyindanyl)-N-hydroxyurea;
N-1-(4-(4-Flurophenoxyindanyl)-N-hydroxyurea;
N-3-(7-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyurea;
N-1-[5-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Pyridinylmethoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea;
N-1-[6-(2-Benzimidazolylmethoxy)-(1,2,3,4-tetrahydronaphthyl)]-N-hydroxyurea; or
N-1-(7-Phenoxyindanyl)-N-hydroxyurea.

11. The compound according to Claim 1 which is N-1-[(5-Phenyloxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea and the pharmaceutically acceptable salts thereof.

12. The compound according to Claim 1 which is N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea and the pharmaceutically acceptable salts thereof.

13. The compound according to Claim 1 which is N-1-[5-(4-Flurophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyurea and the pharmaceutically acceptable salts thereof.

14. The compound according to Claim 1 which is N-1-(5-Phenoxyindanyl)-N-hydroxyurea and the pharmaceutically acceptable salts thereof.

15. The compound according to Claim 1 which is N-3-(6-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyurea and the pharmaceutically acceptable salts thereof.

16. The compound according to Claim 1 which is (-)-N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyurea and pharmaceutically acceptable salts thereof.

17. The compound according to Claim 1 which is (+)-N-3-(6-Benzyloxy-2,3-dihydrobenzofuryl)-N-hydroxyurea and pharmaceutically acceptable salts thereof.

18. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier or diluent and a compound of Claim 1 or a pharmaceutically acceptable salt thereof.

19. A method of treating an OPUFA mediated disease in a mammal in need thereof, which process comprises administering to such mammal an effective OPFUA inhibiting amount of a compound according to Claim 1, or pharmaceutical salt thereof .

20 . The method according to Claim 19 wherein the enzyme 5-lipoxygenase is inhibited.

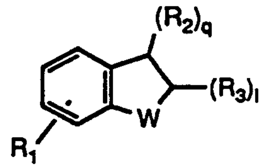
21. The method according to Claim 20 wherein W is $CH_2(CH_2)_s$ or $O(CH_2)_s$, and s is a number having a value of 0 or 1.

22. The method according to Claim 21 wherein B is oxgyen and q is 1.

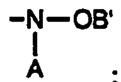
23. The method according to Claim 19 wherein the lipoxygenase mediated disease is arthritis, rheumatoid arthritis, osteoarthritis, allergic rhinitis, psoriasis, dermatitis, ischemic induced myocardial injury, reperfusion injury, gout, asthma, adult respiratory distress syndrome, atherosclerosis, inflammatory bowel disease, stroke, spinal cord injury or traumatic brain injury.

24. A method of treating algesia in an animal in need thereof which comprises administering to said mammal an effective analgesic amount of a compound according to Claim 1 or a pharmaceutically acceptable salt thereof.

25. A compound of the formula



(II)

wherein R_2 and R_3 are  ;

B' is hydrogen, benzyl, optionally substituted benzyl , $Si(R_x)_3$, $C(O)R_{5'}$, $C(O)OR_{5'}$, $CH_2OCH_2CH_2Si(Rx3)_3$, C_1alkyl-C_{1-3}alkoxy, and C_1alkylC_2alkoxyC_{1-3}alkoxy, or tetrahydropyranyl ;

$R_{5'}$ is C_{1-6} alkyl, aryl, or aralkyl;

A is hydrogen or $C(O)OR_z$;

R_z is benzyl, $Si(R_x)_3$, t-butyl, $CH_2OCH_2CH_2Si(CH_3)_3$;

R_x is independently selected from C_{1-6} alkyl or aryl;

W is $CH_2(CH_2)_s$, $O(CH_2)_s$, $S(CH_2)_s$, or $NR_9(CH_2)_s$;

R_9 is hydrogen, C_{1-4} alkyl, C_{1-6} alkoyl, or aroyl;

s is a number having a value of 0 to 3;

q is a number having a value of 0 or 1;

l is a number having a value of 0 or 1;

provided that when q is 0 then l is 1 and R_2 is hydrogen and when q is 1 then l is 0 and R_3 is hydrogen;

R_1 is a member selected from the group consisting of hydrogen, alkyl $_{1-10}$, alkoxy $_{1-10}$, $(CH_2)_m$-Ar-$(X)_v$, $O(CH_2)_m$Ar-$(X)_v$, $S(CH_2)_m$-Ar-$(X)_v$, or $N(CH_2)_m$-Ar-$(X)_v$;

m is a number having a value of 0 to 3;

n is a number having a value of 0 to 3;

v is a number having a value of 1 to 3;

Ar is a member selected from the group consisting of phenyl, napthyl, quinolyl, isoquinolyl, pyridyl, furanyl, imidazoyl, benzimidazoyl, triazolyl, oxazolyl, isoxazolyl, thiazole, or thienyl;

X is a member selected from the group consisting of hydrogen, halogen, alkyl $_{1-10}$, cycloalkyl $_{5-8}$, alkenyl $_{2-10}$, hydroxy, $(CHY)_t$carboxy, O-alkyl $_{1-10}$, S-alkyl $_{1-10}$, SO-alkyl $_{1-10}$, SO_2-alkyl $_{1-10}$, aryloxy, arylalkyl$_{1-6}$ oxy, halosubstituted alkyl$_{1-6}$, $(CHY)_tN(R_5)_2$ or cyano; provided that if v is a number greater than 1 then one substituent must be selected from alkyl, O-alkyl $_{1-10}$, or halo;

Y is hydrogen or alkyl$_{1-3}$;

t is 0 or 1; provided that when B is hydrogen, W is other than $CH_2(CH_2)_s$, and s is 0 or 1, and B is hydrogen, W is other than $S(CH_2)_s$ and s is 1;

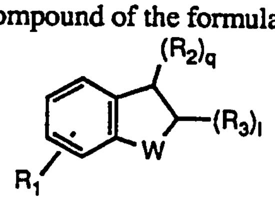
and the pharmaceutically acceptable salts thereof.

26. The compound according to Claim 25 which is
N-1-(5-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-(5-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-[5-(4-Flurophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine;
N-1-(6-Benzyloxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-(6-Phenoxy-1,2,3,4-tetrahydronaphthyl)-N-hydroxyamine;
N-1-[6-(4-Fluorophenoxy)-1,2,3,4-tetrahydronaphthyl]-N-hydroxyamine; or
N-1-(5-Benzyloxyindanyl)-N-hydroxyamine;
N-1-(5-Phenoxyindanyl)-N-hydroxyamine;
N-1-(5-(4-Flurophenoxyindanyl)-N-hydroxyamine;
N-1-(4-Benzyloxyindanyl)-N-hydroxyamine;
N-1-(4-Phenoxyindanyl)-N-hydroxyamine;
N-1-(4-(4-Flurophenoxyindanyl)-N-hydroxyamine;
N-3-(7-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine;
N-3-[7-(4-Flurophenoxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine; or
N-3-(7-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine.
N-3-(6-Phenoxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine;
N-3-[6-(4-Flurophenoxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine; or
N-3-(6-Benzyloxy-2,3-dihydrobenzofuranyl)-N-hydroxyamine.

27. A method of treating an OPUFA mediated disease in a mammal in need of such treatment which comprises administering to said mammal an effective OPFUA inhibiting amount of a compound according to Claim 25 or a pharmaceutically acceptable salt thereof.

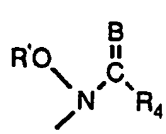
28. The method according to Claim 27 wherein the OPUFA mediated disease is ischemia induced myocardial injury, reperfusion injury, stroke, traumatic brain injury or spinal cord injury.

29. A process for producing a compound of the formula



(I)

wherein

R_2 and R_3 are  ;

R' is hydrogen, a pharmaceutically acceptable cation, aroyl or a C_{1-12} alkoyl;

B is oxygen or sulfur;

R_4 is NR_5R_6, alkyl $_{1-6}$, halosubstituted alkyl $_{1-6}$, hydroxy substituted alkyl $_{1-6}$, alkenyl $_{2-6}$, aryl or heteroaryl optionally substituted by halogen, alkyl $_{1-6}$, halosubstituted alkyl$_{1-6}$, hydroxyl, or alkoxy $_{1-6}$;

R_5 is H or alkyl$_{1-6}$;

R_6 is H, alkyl$_{1-6}$, aryl, benzyl, heteroaryl, alkyl substituted by halogen or hydroxyl, or phenyl substituted by a member selected from the group consisting of halo, cyano, alkyl$_{1-12}$, alkoxy $_{1-6}$, halosubstituted alkyl$_{1-6}$, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R_5 and R_6 may together form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen;

W is $CH_2(CH_2)_s$, $O(CH_2)_s$, $S(CH_2)_s$, or $NR_7(CH_2)_s$;

R_7 is hydrogen, C_{1-4} alkyl, phenyl, C_{1-6} alkoyl, or aroyl;

s is a number having a value of 0 to 3; provided that when l is one and W is $O(CH_2)_s$, $S(CH_2)_s$, then s is 1 to 3; and when W is $NR_7(CH_2)_s$ then s is 1 to 3 and q is 1;

q is a number having a value of 0 or 1;

l is a number having a value of 0 or 1;

provided that when q is 0 then l is 1 and R_2 is hydrogen; and when q is 1 then l is 0 and R_3 is hydrogen;

R_1 is a member selected from the group consisting of hydrogen, alkyl $_{1-10}$, alkoxy $_{1-10}$, $(CH_2)_m$-Ar-$(X)_v$, $O(CH_2)_m$Ar-$(X)_v$, or $S(CH_2)_m$-Ar-$(X)_v$;

m is a number having a value of 0 to 3;

v is a number having a value of 0 to 3;

Ar is a member selected from the group consisting of phenyl, napthyl, quinolyl, isoquinolyl, pyridyl, furanyl, imidazoyl, benzimidazoyl, triazolyl, oxazolyl, isoxazolyl, thiazole, or thienyl;

X is a member selected from the group consisting of hydrogen, halogen, alkyl $_{1-5}$, cycloalkyl $_{5-8}$, hydroxy, $(CHY)_t$carboxy, O-alkyl $_{1-5}$, $S(O)_r$ alkyl $_{1-5}$, halosubstituted alkyl$_{1-6}$, $(CHY)_tN(R_5)_2$ or cyano; provided that if v is a number greater than 1 then one substituent must be selected from alkyl, O-alkyl $_{1-5}$, or halo;

r is a number having a value of 0 to 2;

Y is hydrogen or alkyl$_{1-3}$;

t is a number having a value of 0 or 1;

and the pharmaceutically acceptable salts thereof

which process comprises:

A. reacting a compound of Formula (II) as described above, wherein B is Hydrogen,

(i) with trimethylsilyl isocyanate (TMSNCO), followed by work up with ammonium chloride to yield a hydroxyurea derivative of a Formula (I) compound wherein R_4 is NH_2; or

(ii) with sodium or potassium cyanate in an acidic solution to yield a hydroxyurea derivative of a Formula (I) compound wherein R_4 is NH_2; or

(iii). with gaseous HCl, followed by treatment with phosgene or phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate resulting in the corresponding carbamate; which is reacted with aqueous ammonia, or substituted amine to yield an optionally substituted hydroxyurea derivative of a Formula (I) compound; or

(iv) with acetyl chloride and organic solvent, such as triethylamine to yield the N,O-diacetate derivative followed by hydrolysis with an alkali hydroxide, such as lithium hydroxide, to yield a compound of Formula (I) wherein R_4 is other than NR_5R_6; or

(v) with an acylating agent, such as acetic anhydride in the presence of a base, such as pyridine, followed by hydrolysis with an alkali hydroxide, such as lithium hydroxide, to yield a compound of Formula (I) wherein R_4 is a hydroxamic acid derivative; or

B. reacting a compound of Formula (II) as described above, wherein B is a benzyl, substituted benzyl or benzyl carbonate protecting group, with

(i) acetyl chloride in organic solvent to yield a protected hydroxamic acid derivative of Formula (I) compounds, which is then deprotected, optionally by hydrogenation or with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I) wherein R_4 is other than NR_5R_6; or

(ii) trimethylsilyl isocyanate as in step A above, to yield protected hydroxyurea derivatives of Formula (I) compounds which is then deprotected, optionally by hydrogenated with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I); or

(iii) phosgene or phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or substituted amine; which is then deprotected, optionally by hydrogenation or with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I); or

(iv) sodium or potassium cyanate in an acidic solution and is then deprotected, optionally by hydrogenation or with ethane thiol in the presence of aluminium trichloride, to yield a compound of Formula (I); or

C. reacting a compound of Formula (II) as described above, wherein B is is $Si(R_x)_3$, or $CH_2OCH_2CH_2Si(Rx)_3$with

(i) sodium or potassium cyanate in an acidic solution , as described in Step A above and deprotected by use of anhydrous fluoride $(R_4N^+)F^-$, or under mildly acidic conditions; or ;

(ii) phosgene or phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or substituted amine; which is deprotected by use of anhydrous fluoride $(R_4N^+)F^-$, or under mildly acidic conditions; or

(iii) trimethylsilyl isocyanate as in step A above and then deprotected by use of anhydrous fluoride $(R_4N^+)F^-$, or mildly acidic conditions; or

(iv) acetyl chloride in organic solvent which is then deprotected by use of anhydrous fluoride $((R_4N^+)F^-$, or under mildly acidic conditions to yield the corresponding compounds of Formula (I); or

D. reacting a compound of Formula (II) as described above, wherein B is tetrahydropyranyl, C_1alkyl-C_{1-3}alkoxy, or C_1alkylC_2alkoxyC_{1-3}alkoxy, with

(i) sodium or potassium cyanate in an acidic solution , as described in Step A above and deprotected by a mild acid treatment, such as pyridinium para-toulenesulphonate in methanol or dilute HCl; or

(ii) phosgene or phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or substituted amine; and deprotected by a mild acid treatment, such as pyridinium para-toulenesulphonate in methanol or dilute HCl; or

(ii) with trimethylsilyl isocyanate as in step A above and deprotected by a mild acid treatment, such as pyridinium para-toulenesulphonate in methanol or dilute HCl; or

(iii) with acetyl chloride in organic solvent which is then deprotected by a mild acid treatement, such as pyridinium para-toulenesulphonate in methanol or dilute HCl to yield the corresponding compounds of Formula (I); or

E. reacting a compound of Formula (II) as described above, wherein B is t-butyloxycarbonyl with

(i) sodium or potassium cyanate in an acidic solution, and deprotected by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or with anhydrous ether HCl; or

(ii) phosgene or phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or substituted amine; and deprotected by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or with anhydrous ether HCl; or

(iii) with trimethylsilyl isocyanate and then reacted with ethane thiol in the presence of aluminium trichloride as in step I.; and deprotected by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or anhydrous ether HCl; or

(iv) with acetyl chloride in organic solvent which is then deprotected, optionally with ethane thiol in the presence of aluminium trichloride; or by treatment with trifluroracetic acid, trimethylsilyltrifilate with 2,6-lutidine, or anhydrous ether HCl to yield the corresponding compounds of Formula (I); or

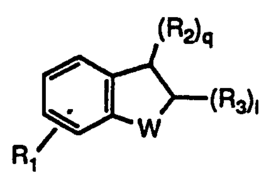
F. reacting a compound of Formula (II) as described above, wherein B is an alkoyl or aroyl with

(i) sodium or potassium cyanate in an acidic solution , as described in Step B above; and deprotected with a suitable base, such as potassium carbonate; or

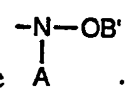
(ii) with trimethylsilyl isocyanate as in step A above and deprotected with a suitable base, such as potassium carbonate; or

(iii) with acetyl chloride in organic solvent which is then deprotected by treatment with a suitable base, such as potassium carbonate; to yield the corresponding compounds of Formula (I).

30. A process for producing a compound of the formula



(II)

wherein R_2 and R_3 are  ;

B' is hydrogen, benzyl, optionally substituted benzyl , $Si(R_x)_3$, $C(O)R_{5'}$, $C(O)OR_{5'}$, $CH_2OCH_2CH_2Si(R_{x3})_3$, C_1alkyl-C_{1-3}alkoxy, and C_1alkylC_2alkoxyC_{1-3}alkoxy, or tetrahydropyranyl ;

$R_{5'}$ is C_{1-6} alkyl, aryl, or aralkyl;

A is hydrogen or $C(O)OR_z$;

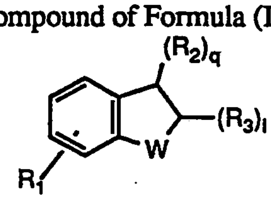
R_z is benzyl, $Si(R_x)_3$, t-butyl, $CH_2OCH_2CH_2Si(R_x)_3$;

R_x is independently selected from C_{1-6} alkyl or aryl;

W is $CH_2(CH_2)_s$, $O(CH_2)_s$, $S(CH_2)_s$, or $NR_9(CH_2)_s$;
R_9 is hydrogen, C_{1-4} alkyl, C_{1-6} alkoyl, or aroyl;
s is a number having a value of 0 to 3;
q is a number having a value of 0 or 1;
l is a number having a value of 0 or 1;
provided that when q is 0 then l is 1 and R_2 is hydrogen and when q is 1 then l is 0 and R_3 is hydrogen;
R_1 is a member selected from the group consisting of hydrogen, alkyl $_{1-10}$, alkoxy $_{1-10}$, $(CH_2)_m$-Ar-$(X)_v$, $O(CH_2)_m$Ar-$(X)_v$, $S(CH_2)_m$-Ar-$(X)_v$, or $N(CH_2)_m$-Ar-$(X)_v$;
m is a number having a value of 0 to 3;
n is a number having a value of 0 to 3;
v is a number having a value of 1 to 3;
Ar is a member selected from the group consisting of phenyl, napthyl, quinolyl, isoquinolyl, pyridyl, furanyl, imidazoyl, benzimidazoyl, triazolyl, oxazolyl, isoxazolyl, thiazole, or thienyl;
X is a member selected from the group consisting of hydrogen, halogen, alkyl $_{1-10}$, cycloalkyl $_{5-8}$, alkenyl $_{2-10}$, hydroxy, $(CHY)_t$carboxy, O-alkyl $_{1-10}$, S-alkyl $_{1-10}$, SO-alkyl $_{1-10}$, SO_2-alkyl $_{1-10}$, aryloxy, arylalkyl$_{1-6}$ oxy, halosubstituted alkyl$_{1-6}$, $(CHY)_tN(R_5)_2$, or cyano; provided that if v is a number greater than 1 then one substituent must be selected from alkyl, O-alkyl $_{1-10}$, or halo;
Y is hydrogen or alkyl$_{1-3}$;
t is 0 or 1; provided that when B is hydrogen, W is other than $CH_2(CH_2)_s$, and s is 0 or 1, and B is hydrogen, W is other than $S(CH_2)_s$ and s is 1;
and the pharmaceutically acceptable salts thereof

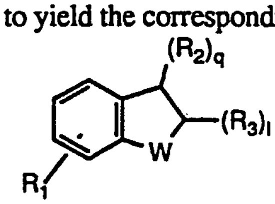
which process comprises

A. reacting a compound of Formula (III)



(III)

wherein
R_2 and R_3 are =O;
W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);
with hydroxylamine in solvent to yield the corresponding oxime derivative of Formula (IV)

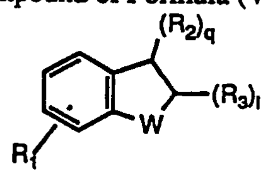


(IV)

wherein
R_2 and R_3 are =N-OH;
W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);
which is then reduced with borane pyridine complex, borane trimethylamine, or borane tetrahydrofuran or other borane complexes, to yield the hydroxylamine derviatives of Formula (II); or

B. reacting a compound of Formula (IV) as defined above with sodium cyanoborohydride or phenyldimethylsilane in anhydride in trifluroacetic acid to yield the hydroxylamine derviatives of Formula (II); or

C. reacting a compound of Formula (V)

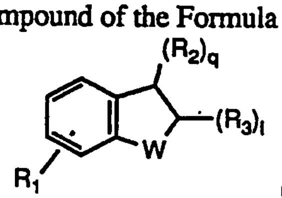


(V)

wherein
R_2 and R_3 are X;
X is a leaving group;
W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);
with Z-furfulaldehyde oxime and base to yield the corresponding nitrone of Formula (VI) which is hydroylzed to yieldthe hydroxylamine derviatives of Formula (II);

D. reacting a compound of Formula (V) with a protected hydroxylamine to yield the corresponding protected hydroxylamine of Formula (II); or

E. reacting a compound of the Formula (VI)



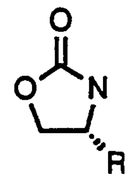
(VI)

wherein
R_2 and R_3 are OH;
W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II) as described above;
with a protected hydroxylamine, such as N,O-bis(t-butyloxycarbonyl)-hydroxylamine) or bisbenzyloxycarbonyl, and triphenylphosophine/ diethyldiazodicarboxylate to produce an intermediate which is treated with acid to yield the hydroxylamines of Formula (II).

31. The process according to Claim 30, Step C. wherein the leaving group is halogen, tosylates, mesylates or a triflates moiety; and the hydrolysis is by hydroxylamine or under acidic conditions.

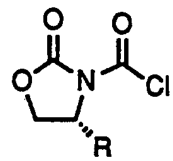
32. A process for making the chiral compounds of Formula (I) as described above which process comprises

A. (i) reacting a homochiral oxazolidione of Formula (A)



(A)

wherein R is an optionally substituted aryl, arylmethyl, heteroaryl, or heteroarylmethyl; with phosgene or a phosgene equivalent and base in anhydrous solvent to yield to form the corresponding acid chloride intermediate of Formula (VII)



(VII)

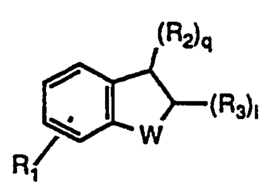
(ii) reacting the Formula (VII) adduct with a chloronated hydrocarbon or etheral solvent and base to yield the corresponding (+) and (-) compound of Formula (II);

(iii) cleaving the adducts under basic conditions to yield the individual entantiomers of the Formula (II) compounds; or

B. reacting (i) an optically active alcohol of Formula (VI) as defined above with N,O-bis(t-butyloxycarbonyl)hydroxylamine) and triphenylphosophine/ diethyldiazodicarboxylate to produce an intermediate which is treated with acid to yield the hydroxylamines of Formula (II); or

(ii) reacting the corresponding optically active halo or sulfonate of Formula (VI), which may be optionally protected in a base, such as triethylamine, pyridine to yield the corresponding chiral Formula (II) compounds; or

C. (i) reacting an optically active amine of Formula (VIII)



(VIII)

wherein

R_2 and R_3 are NH_2;
W, R_1, R_7, s, q, l, m, v, Ar, S, t, and Y are as defined for Formula (II);
with 4-methoxybenzaldehyde in trimethylamine;

(ii) oxidizing the intermediate of step (i) to yield the corresponding oxaziridine;

(iii) reacting the oxaziridine of step (ii) under acid conditions to yield the hydroxylamine salts of Formula (II) compounds; or

D. reacting the optically active amine of Formula (VIII) as described above with dimethyldioxirane or a peracid anhydride, such as benzoyl peroxide, to yield the protected chiral hydroxylamine of Formula (II) compounds; which may be optionally deprotected to yield the final compounds of Formula (II).

33. The process according to Claim 32, Part A. (i) wherein the R is an optionally substitututed phenyl; the base in step (i) is NaH, the anhydrous solvent is toluene and the solution is cooled to about -70°C to about 20°C.

34. The process according to Claim 33 wherein base of step (ii) is an amine base, such as trialkylamine or pyridine, or is a solid alkali metal carbonate, such as calcium carbonate or potassium carbonate.

35. The process according to Claim 34 wherein the adduct is cleaved in step (c) by an alkali metal hydroperoxide, such as lithium hydroperoxide.

36. The process according to Claim 35 wherein the cleavage occurs in an aqueous-etheral solvent such as tetrahydrofuran, glyme, diglyme or ethyl ether, at a temperature of about -20°C to about 50°C.